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GIANT-CELL TUMORS OF BONE*

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IN 1920 Dr. E. A. Codman, of Boston, organized the Registry of Bone Sarcoma. A committee consisting of Dr. Codman, Dr. Ewing and Dr. Bloodgood studied a large number of cases of bone tumors, and from them they separated a group of benign giant-cell tumors. Up to that time many limbs had been amputated on the supposition that a giant-cell tumor was a malignant condition. With its benignity thus well established Dr. Codman§ laid down certain general principles deduced from his study:

> The expansion and progress of these tumors is due to their pulsation, not to the malignant quality of their cells. Therefore, we should pay scrupulous attention to stopping their blood supply.
>
> The persistence of a large cavity in the bone is one main reason for the inadequacy of the modes of treatment in vogue. Therefore, we should collapse the bony wall of the cavity and by using a flap of periosteum we may make the defect outside instead of inside the cortex.
>
> We should bear in mind Wolff's law: that regeneration of bone tends to occur in lines of stress and absorption tends to take place where there is no stress. Therefore, we should place periosteum where new bone will be formed on the concave side of the defect, from which the tumor has been removed.
>
> After operation we should support the limb, not only to prevent fracture, but in a manner that will assure stress in the normal line of weight bearing.
>
> We should not jeopardize the normal repair process by the use of chemical or electrical cautery or by radiation.

Codman suggested that a subperiosteal resection of the tumor be carried out and that the cavity thus made be obliterated by infolding of periosteum. He reported a case of giant-cell tumor of the upper end of the tibia treated in this way (Fig. 1). The immediate results in this case were quite satisfactory, and the patient obtained full use of her limb. Unfortunately, she later died of a recurrence of the tumor, which apparently was malignant from the onset. The method used, however, was impressive.

In giving the details of the operation, Dr. Codman pointed out that the normal bone should be entered at a considerable distance from the tumor and the medulla should be well exposed beyond the junction of the tumor and the bone marrow. The reason for this is the importance of observing the concavo-convex boundary line between tumor and normal bone, which he considered so constant in giant-cell tumors as to be diagnostic. So strongly did he feel about this that he said that, if this concavo-convex boundary were not found at exploration and if the tumor extended into bone marrow, the surgeon should amputate at once. He also pointed out that obliteration of the cavity offered more chance of regeneration of the bone than curettage of the cavity and the use of blood clot and bone chips to obliterate it.

Before this, curettage had been carried out for many such tumors, and a chemical, usually carbolic acid, had been used to destroy any remaining cells. Codman decided not to use any chemicals. It is an interesting point, and an important one, that a giant-cell tumor can be cured by curettage, for it is obvious that, without chemical cauterization, all cells are not removed. Similarly, the operation described by Codman does not remove all cells, and yet the tumor can be successfully eradicated. There must be something about the giant-cell tumor of bone that is different from other tumors. However, in 1 of our cases we demonstrated that cells could be implanted in the operative wound and continue to grow there, indicating that it was a real tumor.

We are presenting the reports of 7 patients operated on for benign giant-cell tumors. In 5 cases Codman's method of reflecting periosteum and curetting the tumor was used. In 1 additional case curettage was done, and in the other curettage and bone graft was the method used.

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§Codman, E. A. Treatment of giant-cell tumors about knee. *Surg., Gynec. & Obst.* **64**:485-496, 1937.

Case Reports

Case 1 (M.G.H. 234660). A 23-year-old telephone operator was examined on February 23, 1940, with the chief complaint of a dull, steady, aching pain in the region of the right knee that had begun 1 year previously. The pain remained constant, irrespective of position, weight bearing or motion. Two months later tenderness had been noted along the medial aspect of the knee. For the past 2 months she had been unable to extend the right knee fully, and she also had pain on acute flexion. There was no history of trauma except for a slight injury from a fall from a bicycle 3 years before, with a little discomfort lasting for 2 or 3 days only.

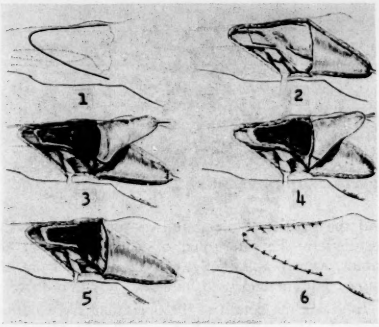


Figure 1. *Subperiosteal Resection of a Giant-Cell Tumor (Reproduced from Codman, E. A., Surg., Gynec. & Obst. 64:485-496, 1937, with the Permission of the Publishers).* 1 = *the skin incision.* 2 = *the periosteal flap outlined.* 3 = *the periosteal flap reflected and the tumor exposed (note the concavo-convex junction of the tumor and the bone).* 4 = *the tumor curetted from the cavity.* 5 = *infolding of the periosteal flap.* 6 = *skin closure.*

Physical examination was negative except for tenderness along the medial aspect of the right knee and slight swelling in the same area. No mass was palpable.

X-ray examination showed a well defined area of decreased density, involving the posterior portion of the medial condyle of the right femur. This area extended down to the joint surface, which, however, was intact. Some septums were seen within the abnormal area. The findings were consistent with giant-cell tumor of bone (Fig. 2*A*).

At operation on March 5, exploration, excision and curettage of a giant-cell tumor were carried out. An incision was made over the medial aspect of the femur, extending down to the condyle. The muscle fibers were split, and the bone was exposed. The periosteum over the condyle was adherent; a flap of periosteum was turned back. The tumor mass was entered and was found to be soft and vascular, with an eggshell segment of cortex overlying it. The tumor was removed by thorough curetting of the cavity. The cavity was smooth, and its proximal end was concave. The shell of the medial condyle was then collapsed, and the previously constructed periosteal flap was turned down into the cavity and held in place by transplanted muscle. The wound was closed in layers, and a full-length cast was applied.

Pathological examination showed a benign giant-cell tumor of the bone. The patient made a good recovery. Five months after operation she was walking well without pain and with normal knee motion.

In October, 1944, x-ray study disclosed a cavity suggesting a recurrence of tumor proximal to the treated area. There were no symptoms or abnormal physical findings. A second operation was performed. The old incision was excised; a window was made in the cortex of the medial condyle, and the contents of the cavity, consisting of some soft tissue suggestive of tumor and soft bone, were curetted out. Normal bone was found at the proximal end. Pathological examination revealed normal bone and no tumor.

The patient continued to do well, with excellent function, no symptoms and no evidence of recurrence. She was last seen 14 years after operation (Fig. 2*B*).

Case 2 (P. H. 12171). A 21-year-old female domestic was examined on March 10, 1937, with a history of swelling of the sternal end of the left clavicle. This had started to develop shortly after an injury to this region from a fall 5 years before. The swelling had persisted and had gradually increased. There was no pain.

Physical examination was negative except for a hard, slightly irregular fusiform swelling in the sternal end of the left clavicle, measuring about 6 by 10 cm. There was no tenderness.

X-ray examination revealed, in the medial third of the left clavicle, an extensive area of bone rarefaction, with

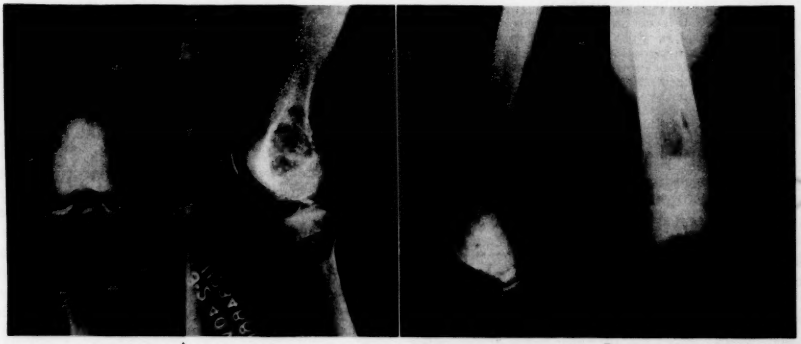


Figure 2. *Giant-Cell Tumor of the Lower Portion of the Right Femur in Case 1* (A), *with the Appearance Fourteen Years after Operation* (B).

definite bulging but without complete destruction of the cortex. There was no evidence of extension into the soft tissues. The diagnosis was a benign bone tumor.

On March 15 a curved incision was made below the tumor mass and was carried down through muscle to the periosteum; a large periosteal flap with its base at the sternal end was reflected. The tumor was a cystic mass with a paper-thin cortex. The top of the cyst was lifted off; bluish tumor tissue was removed, and the cavity was thoroughly curetted. The sides of the cyst were broken down, and the periosteum was packed into the cavity. The cavity was obliterated by turning in of the muscles. The wound was closed without drainage. A figure-of-8 plaster bandage was applied. The patient did well postoperatively and was discharged 2 weeks later with the figure-of-8 plaster in place.

Pathological examination was reported as follows:

> Soft, red pieces of tissue show small, grayish-white, firm areas. On microscopical study granulation tissue with a moderate number of lymphocytes and giant cells is seen. The giant cells have many small vesicular nuclei. The diagnosis is benign giant-cell tumor or osteitis fibrosa cystica, with foci of cartilage and apparent osteoid formation.

Later, this was pronounced a giant-cell tumor.

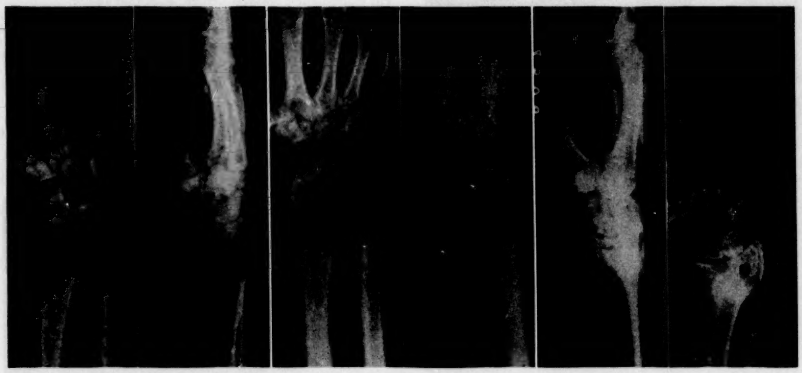
The cast was removed in 6 weeks, and the clavicle felt solid. The patient had excellent function and no symptoms. She has continued to do well and the clavicle is solid. X-ray studies in October, 1947 (10 years after operation), showed the inner end of the left clavicle to be somewhat broadened, with a small area of rarefaction. She was seen 11 years after operation with no clinical evidence of recurrence and no symptoms.

The next 2 cases of giant-cell tumor of the right radius were of some interest in that the patients were seen at about the same time in the same hospital. One had x-ray treatment and later an operation, and the other was treated immediately by operation. The results at the end of ten years are very satisfactory from a functional point of view, although in each case the appearance of the wrist and of the x-ray films indicates a poor operative result.

Case 3 (W.S.,C.S., 4506). A 35-year-old house painter and decorator was examined on September 10, 1941. He had noticed slight swelling of the right wrist, with persistent pain and weakness for 6 weeks. There was no history of trauma.

Physical examination showed fullness in the region of the distal end of the right radius, with weakness in the wrist. A diagnosis was not made until an x-ray film had been taken.

On x-ray examination the right wrist demonstrated a sharply circumscribed, osteolytic lesion measuring approximately 3 by 2 by 2 cm. and involving the medial portion of the distal end of the radial shaft up to its articular surface. There was slight irregularity of the proximal border of this lesion (Fig. 3*A*). On a 2d examination it was noted that the margins of the lesion were quite irregular; yet the cortex was preserved, although it was markedly thin. A diagnosis of giant-cell tumor was made.



A B C

Figure 3. *Giant-Cell Tumor of the Lower End of the Right Radius in Case 3 before Treatment* (A) *and Five Months Later—Three and a Half Months after X-Ray Treatment* (B). *Nine years after operation there was marked radial shortening* (C) *but good function.*

X-ray treatment was advised; 1800 r was given at the rate of 300 r per day, 250 K.V., through a 5-cm. portal, being given to the dorsal aspect of the radius. Three weeks later a similar amount was given to the volar aspect. After treatment the pain was less. Three and a half months after the treatment had been completed, the patient still was free from pain. X-ray examination (Fig. 3*B*) showed no response in the bone, and there was a slight increase in the involved area. Operation was then decided on.

On February 11, 1942, an incision was made over the radial aspect of the tumor at the lower end of the radius. The tumor was broken into and curetted. The tissue was friable and firmer than the usual giant-cell tumor. The periosteal flap was pressed in to obliterate the cavity as far as possible; 2 gm. of sulfanilamide was placed in the wound, and the skin was closed without drainage. A plaster cast was applied in an attempt to obtain normal position of the hand.

The pathological report was as follows:

> On microscopical examination of numerous pieces of granular bony tissue, aggregating in total 2 by 2 by 1 cm., no definite tumor is seen. The softer curettings consist of fibrous tissue, containing numerous capillaries and a few polymorphonuclear leukocytes; frequent mononuclear cells are scattered throughout. The areas near the bone show fibrosis only. The diagnosis is fibrosis and chronic inflammation compatible with radiation reaction in a giant-cell tumor.

As soon as the wound had healed, a leather gauntlet was made. It was immediately apparent that there was going to be foreshortening of the bone as it healed, with deviation of the hand toward the radial side. The deformity increased in spite of every effort to prevent it. One year later it was learned that the patient was continuing with his work as a painter and that he had an excellent grip. When last seen on January 7, 1953, nearly 11 years after operation, he had a deformity of the wrist, with marked radial shortening. Flexion at the wrist was restricted to about 20 per cent. He had an excellent grip and continued actively as a house painter. X-ray examination (Fig. 3*C*) gave no suspicion of recurrence.

FIGURE 4. *Giant-Cell Tumor of the Lower End of the Right Radius in Case 4 before Operation.*

It is probable that this tumor was completely destroyed by irradiation and that the patient would have had a satisfactory result without curettage. Whether or not he would have required operation to obliterate the cavity is uncertain. Codman pointed out that one must expect a temporary enlargement of the tumor after x-ray treatment.

CASE 4 (W.S.,C.S., 4739). A 25-year-old housewife was examined on November 19, 1941. She had noted swelling of the right wrist for 8 months, with a gradual increase in size. Five months before admission she had fallen and hurt the wrist, and the swelling had increased rapidly since then. A biopsy had been done at another institution, and a diagnosis of giant-cell tumor had been made.

Examination showed a fusiform swelling of the right wrist and marked limitation of motion. X-ray treatment was considered, but was decided not to be wise; operation was advised. She was admitted to the hospital on January 13, 1942, when the tumor was described as about 7 cm. in diameter, with local heat noticeable in the lesion (Fig. 4). Dorsiflexion and palmar flexion were greatly limited.

On January 14 an incision was made over the radial aspect of the tumor, and the tendons and muscles were retracted. The lesion was found to extend through the bone in the region of the old biopsy scar, making it necessary to discard much of the overlying periosteum. The tumor was removed by thorough curettage. The periosteum was then pressed down into the cavity in an effort to obliterate the cavity. The skin was closed without drainage.

Microscopical examination disclosed a benign giant-cell tumor.

As soon as the wound had healed, a leather gauntlet was made, but it was immediately apparent that radial shortening would develop. The patient was able to return home and care for her family of 5 children. One year later, in February, 1943, x-ray examination showed apparent recurrence in the edges of the operative area. A 2d operation was advised.

On March 17 the old scar was reopened, and a tumor mass, 2 cm. in diameter, was found and curetted. Pathological examination showed benign giant-cell tumor.

On August 4 of the same year a further recurrence was noted on x-ray study. At operation on that date the old operative scar was excised, and a cystic area was found on the volar aspect of the radius. The wall was broken down; the cystic cavity was again curetted, and the overlying bone was broken down in an effort to obliterate the cavity. The wound was then closed without drainage.

Pathological examination was reported as showing "benign giant-cell tumor, with an unusual amount of fibrosis and bone formation."

During the last few years the patient has continued with her work at home. She has good function of her wrist, with good dorsiflexion and palmar flexion but with marked radial deviation. She was last examined on January 7, 1953, when the condition was satisfactory, without evidence of recurrence (Fig. 5). This was 9½ years after the last operation.

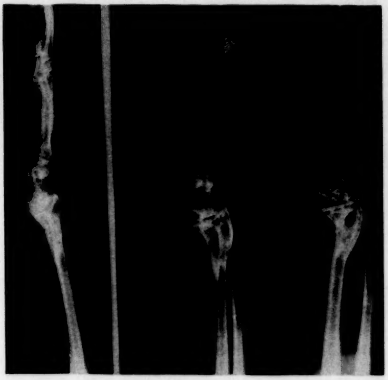


FIGURE 5. *Result in Case 4 Eight Years after Operation. There was marked radial shortening, but good function.*

Resection of the lower end of the radius with a bone graft would probably have given a better cosmetic result and a better anatomic position of the hand. It is doubtful if better function would have been obtained.

CASE 5 (P.H. 20726). A 21-year-old housewife was examined on September 11, 1942, because of a fall on the ice 8 months previously, followed by painful swelling of the right knee. This had been treated by local applications and several months later by a cast. She had fallen again 1 month before admission. The knee had become more painful, and she had been operated on in another hospital. A pack had been left in the wound, and she had been discharged 5 days before admission.

Physical examination showed a pale young woman with a cast on the right lower extremity. A window in the cast revealed foul drainage on the dressing covering the recent wound over the medial condyle of the right femur.

X-ray examination on September 12 showed a large, rounded bone defect involving the lower end of the femur, with extensive rarefaction in the region of the medial condyle, the intercondylar ridges and the lower end of the shaft (Fig. 6*A*). There was evidence of an old fracture. She was treated for the infection.

On November 30 the old scar was excised, and the dissection was carried down to the operative defect in the medial aspect of the condyle. The cavity was explored and was found to be about two thirds full of tumor. The tumor was curetted as rapidly as possible since there was severe bleeding. The cavity was packed, and a pressure dressing and cast were applied.

Pathological examination was reported as follows:

> The specimen consists of numerous pieces of red-gray and dark-red, coarsely papillary tissue. Microscopical examination shows large numbers of multinucleate giant cells set in a sparse stroma of more elongated fibroblastic cells, with numerous endothelial or monocytic cells. The diagnosis is benign giant-cell tumor.

The patient did well; she was discharged in 3 weeks in a windowed cast and on hypochlorite irrigations. Eighteen months later she had no symptoms, walked with a slight limp, and had had a baby. There was considerable lateral mobility of the knee joint. Orthopedic consultation was obtained a year later, and stabilization of the joint was advised but was refused. She learned to walk in such a way that the instability no longer existed. Her knee function continued to improve, and 10 years after operation there was no sign of recurrence (Fig. 6*B*). She is asymptomatic and walks well without any limp; the only limitation of motion is about 5° of extension.

A B

FIGURE 6. *Giant-Cell Tumor of the Distal Portion of the Left Femur in Case 5 Eight Months after a Pathologic Fracture* (A) *and Eleven and a Half Years after Curettage* (B).

CASE 6 (P.H. 23947). A 14-year-old girl was examined on December 13, 1945. She stated that she had had a fall and a pathologic fracture through a cystic lesion in the lower end of the left femur 6 months previously. An operation had been carried out in another hospital, and a diagnosis of benign giant-cell tumor had been made. She had been referred to the Pondville Hospital for possible x-ray treatment because of faulty union. The leg was still in a cast. X-ray treatment was not recommended; the use of a walking caliper was advised, and she was referred back to her surgical clinic. She was again seen in May, 1946, still in a full cast and with x-ray evidence of extension of disease.

When the cast was removed, marked thickening and swelling about the knee were evident, with a well healed scar over the anterolateral aspect of the distal portion of the left femur. Increased lateral mobility of the knee and considerable limitation of dorsiflexion of the foot were noted. No particular tenderness was present.

X-ray examination showed a large, expanding lesion at the distal end of the femur that had completely destroyed the bony structures in this region. The peripheral rim of bone was extremely thinned out and in some places had completely disappeared (Fig. 7*A*). This was thought to be a benign giant-cell tumor.

At operation on May 20 the previous scar was excised, and the tumor was exposed through a lateral incision; the cavity was entered and was found to contain large amounts of soft, friable tissue. The entire cavity was thoroughly curetted. An osteoperiosteal graft was taken from the right tibia, split in 4 pieces and placed lengthwise in the cavity to maintain the length of the bone. The wound was closed. The leg was placed in traction with 2 Kirschner wires through the tibial crest. Eight months after operation (December, 1946) the patient walked for the 1st time in 2 years, using a brace. Flexion of the knee was much reduced, and there was still some swelling around the knee joint.

The pathological report was as follows:

> Numerous fragments of soft gray, tan, and yellow tissue are present. Microscopical examination shows the tumor to be composed of numerous giant cells having deeply acidophilic cytoplasm and regular vesicular nuclei. The stroma consists of spindle-shaped vesicular cells. There is considerable hemorrhage and some xanthoma cells. The diagnosis is giant-cell tumor.

One year later 2 nodules in the upper end of the scar in subcutaneous tissues and muscle were excised. The pathological diagnosis was recurrent benign giant-cell tumor.

Another partially calcified recurrent mass deep in the upper end of the operative scar was removed in 1948. Benign giant-cell tumor was again the pathological diagnosis. The patient has continued to do well. X-ray studies in 1952 showed no change since previous films in 1948 and 1950. Two strips of grafted bone were still visible. The knee is stable.

The patient was last seen in June, 1955. She walks with a very slight limp, is able to dance and to participate in

active sports, and was recently married. Flexion of the knee is decreased to about 45°. There is normal extension and quadriceps function. She has no symptoms. There is no clinical deformity and no evidence of recurrence (Fig. 7*B*).

CASE 7 (P.H. 34872). A 41-year-old housewife was examined on February 11, 1954. Two months before entry she had noted a swelling on the inner aspect of the right elbow that had caused no symptoms; there had been no apparent change in size.

Physical examination showed a hard, nontender mass apparently arising from the lower end of the right humerus on the medial aspect. There were no enlarged axillary lymph nodes and no peripheral-nerve abnormality.

X-ray examination demonstrated a bony lesion at the lower end of the right humerus, mostly metaphyseal and diaphyseal in location. The main body of the tumor was radiolucent but was limited externally by a thin and well defined shelf of calcific density. Running through the radiolucent tumor mass were thin trabeculae of the same calcific density. The internal margin had caused an erosion of the cortical bone, but the bone beneath the erosion appeared sclerotic. A diagnosis of benign tumor was made, probably a chondromyxoid fibroma.

At operation on February 15 an incision was made on the anterior surface of the right arm just above the elbow joint. The superficial nerve was retracted, and the biceps muscle was exposed. The tumor lay beneath the inner head of the biceps muscle. The muscle was divided, and a portion of it was removed with the tumor. The tumor was soft and friable, but it was easily shelled out from the bone cavity. The cavity was curetted. A thin shell of bone extending part way around the tumor was removed flush with the bone by rongeurs.

One small Penrose drain was placed in the cavity to be removed in 24 hours. The muscles and nerve were allowed to drop back in position. The fascia and skin were then closed.

The pathological report was "benign giant-cell tumor."

After operation there was a partial median-nerve paralysis, but this had disappeared at the last examination in July, 1955, when there was no apparent recurrence and elbow function was normal.

A B

FIGURE 7. *Giant-Cell Tumor of the Distal Portion of the Left Femur in Case 6 Six Months after a Pathologic Fracture* (A) *and Nearly Eight Years Later* (B).

TABLE 1. *Benign Giant-Cell Tumors of Bone.*

CASE NO.	AGE	SITE	TREATMENT	YEARS FOLLOWED	RESULT
	yr.				
1	23	Femur (distal end)	Subperiosteal resection	14	Excellent
2	21	Clavicle	Subperiosteal resection	11	Excellent
3	35	Radius (distal end)	X-ray therapy, followed by subperiosteal resection	11	Good function but poor cosmetic appearance
4	25	Radius (distal end)	Subperiosteal resection	11	Good function but poor cosmetic appearance
5	21	Femur (distal end)	Curettage	10	Excellent
6	14	Femur (distal end)	Curettage & bone graft	10	Excellent
7	41	Humerus	Curettage	1	Too early for evaluation

No attempt was made to make a periosteal flap in this case. Because of the very slight cavitation made in the humerus by the tumor, it was thought that the cavity would be easily obliterated.

DISCUSSION

The treatment in these 7 cases was surgical removal of the tumor, although x-ray treatment had preceded operation in 1 case (Table 1).

The subperiosteal resection, with obliteration of the tumor cavity by infolding of the periosteum, was carried out in 4 cases and with a slightly different technic in a fifth. The tumors were successfully removed in all cases, although two operations for recurrences were required in 1.

Curettage of the cavity containing the tumor was performed in 2 cases in which there was extensive involvement of the lower end of the femur. Bone grafts to maintain the normal length of the bone were used in 1 case. There were recurrences in the operative scar in 1 of these cases, but the tumor was finally successfully removed in both.

The cosmetic results in the 2 cases of involvement of the lower end of the radius were not good, although the function was good. This operation is not so good as a resection and bone graft for tumors in this position.

Curettage of large tumors with complete or nearly complete destruction of the lower end of the femur appeared to be a satisfactory method of treatment. Bone grafts may or may not be necessary.

X-ray treatment was used in only 1 case. The immediate result did not seem good, and surgery was carried out. Microscopical examination showed that the previous therapy had probably destroyed the tumor. This may be a good method of therapy in these cases.

483 Beacon Street

SUMMARY

Seven cases of benign giant-cell tumor are reported. In 5 Codman's technic of reflecting peritoneum and curetting the tumor was used. In the other 2, curettage alone and curettage with bone graft comprised the therapy employed.

TREATMENT OF HYPERTENSIVE EMERGENCIES*

Parenteral Use of Reserpine

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THE effective treatment of hypertension is now possible in the great majority of patients with mild hypertension as a result of the widespread use of Rauwolfia preparations derived from *Rauwolfia serpentina*. Treatment of the severe hypertensive and hypertensive emergencies has been possible since the advent of veratrum and other preparations. Many of these potent drugs left much to be desired in terms of safety and predictability.

This study was undertaken to determine the efficacy of parenteral administration of reserpine in hypertensive crisis and intractable hypertension. This agent, in striking contrast to other drugs available, appeared to have great promise because of a wide margin between the therapeutic and the toxic dose, a central action without great cardiac effect and few reported toxic effects. The veratrum preparations always lower the blood pressure when given intravenously, but their use is complicated by precipitous alterations in blood pressure, vomiting and the necessity for constant observation. The therapeutic effects of these alkaloids by other routes of administration are not consistent and, therefore, not clinically feasible. The second group of agents now available, the ganglionic-blocking agents (such as hexamethonium and pentolinium), also may cause a sudden decrease in the blood pressure. However, because of their location of action, they frequently produce severe constipation and are primarily effective only when the patient is in the upright position. The last group of hypotensive drugs in current use — the adrenergic (peripheral) blocking agents (such as phentolamine and phenoxybenzamine) — are not as effective as either the veratrum or the ganglionic-blocking agents. Their action is unpredictable, sometimes with a considerable and sometimes without any noticeable decrease in blood pressure. Their use is also complicated by the lack of a vasopressor agent to counteract any overdosage.

Preparations of *R. serpentina* have been given by mouth for mild hypertension, with very satisfactory results. One important finding in the use of such preparations was the interval of fourteen to twenty-one days between the start of therapy and clinical effectiveness as manifested by reduction in blood pressure. When reserpine, an alkaloidal derivative, became available for parenteral administration, a prompt effect in all types of hypertension was noted in preliminary trials. Finnerty and Sites[1] obtained impressive results in acute hypertensive emergencies with the parenteral route. The present study was undertaken to establish the effect of parenteral adminis-

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tration of reserpine* in the treatment of hypertensive crisis and intractable hypertension and, secondly, to ascertain the optimum dose and duration of action of the drug so as to make possible a plan for clinical use.

Methods and Materials

Twelve male patients were selected for this study with the primary criterion of a sustained severe hypertension, the diastolic pressure in the recumbent position being 110 or greater (Table 1). All patients had a minimum forty-eight-hour control period. Other-wise, there was no selection because of the duration of the hypertension, and some of the patients had had sustained blood-pressure elevations for at least six months. Throughout the study, these patients were maintained on a general medical ward, on bed rest, receiving a standard diet containing 800 mg. of sodium and 3000 ml. of distilled water daily. Blood pressures were recorded four times daily in both the supine and the upright position, and, during periods of drug administration, the levels were recorded hourly by ward personnel using mercury manometers. Patients previously receiving digitalis, antibiotics or other medications continued on these drugs, but no hypotensive or sedative agents were used during this study.

There were 6 patients with hypertensive cardiovascular disease, 4 with malignant hypertensive cardiovascular disease and 2 with glomerulonephritis (Table 1). The ages varied from twenty-nine to sixty-eight with a mean of fifty-two years. There were 7 Caucasian, 3 Negro and 2 Latin-American patients. The initial blood pressures with the patient supine ranged from 200 to 270 systolic and 110 to 166 diastolic, with a mean of 209 systolic, 131 diastolic. Corollary findings revealed only 1 patient without demonstrable renal disease according to the grading used.

The control determinations of blood urea nitrogen ranged from 15 to 66 mg. per 100 ml., with a mean of 34.7 mg. Blood creatinine determinations varied from 1.3 to 5.1 mg. per 100 ml., with a mean of 2.2 mg. All patients had vascular changes (Keith–Wagener classification) on funduscopic examination, which was done by the Ophthalmology Service in addition to examination by us. Control electrocardiograms revealed 7 patients with hypertrophy of the left ventricle, with strain and ischemia, 3 with hypertrophy with strain and 1 with hypertrophy without strain. One patient showed minimal T-wave changes only.

Table 1. *Data in Hypertensive Patients Receiving Reserpine by Intramuscular Injection.*

Patient	Diagnosis	Age	Race	Initial Blood Pressure		Renal Disease†	Blood Urea Nitrogen	Creatinine	Fundi‡	Electrocardiographic Changes§
				Supine position	Upright position					
		yr.					mg./100 ml.	mg./100 ml.		
B.C.	Malignant hypertensive vascular disease	43	W*	264/150	244/166	+++	64	3.9	4	4
V.A.	Malignant hypertensive vascular disease	46	W	230/140	190/120	+++	41	1.9	3	4
J.N.	Hypertensive cardiovascular disease	68	W	220/130	210/120	++	30	1.7	4	4
T.S.	Malignant hypertensive vascular disease	37	W	220/140	150/110	++	31	1.8	4	4
J.F.	Glomerulonephritis	43	W*	210/130	230/140	++	22	1.8	4	4
G.G.	Glomerulonephritis	29	W	230/160	190/140	+++	40	1.8	3	1
J.D.	Hypertensive cardiovascular disease	55	W	230/150	220/140	++	24	1.7	3	4
H.F.	Hypertensive cardiovascular disease	61	N	250/170	230/146	+++	66	5.1	4	3
J.E.	Hypertensive cardiovascular disease	59	W	200/130	190/110	++	25	1.3	2	3
F.W.	Malignant hypertensive vascular disease	62	N	240/150	220/130	+++	30	2.2	4	4
S.M.	Hypertensive cardiovascular disease	55	N	270/160	220/140	++	28	2.1	2	3
W.M.	Hypertensive cardiovascular disease	65	W	220/110	210/110	+	15	1.3	2	2
Mean		51.9		227/143	209/131		34.7	2.22		

*Latin-American patients.

†Grading of renal disease: +, normal or occasional albuminuria; ++, albuminuria & elevated blood urea nitrogen; +++, albuminuria, elevated blood urea nitrogen & fixed specific gravity.

‡Keith–Wagener classification (graded 1-4).

§Grading of electrocardiograms: Grade 4, hypertrophy of left ventricle, with strain & ischemia; Grade 3, hypertrophy of left ventricle, with strain; Grade 2, hypertrophy of left ventricle, without strain; Grade 1, minimal T-wave changes only.

*Kindly supplied as Serpasil, for parenteral injection, by Ciba Pharmaceutical Products, Summit, New Jersey.

After the control determinations had been completed, each patient was given an initial dose of 2.5 mg. of reserpine intramuscularly. Most of them received more than a single dose, but as noted above, the blood pressure returned to the pretest levels before repeat studies were performed, and there was always a minimum of forty-eight hours between doses. The same technic was used when the patients received doses of 5 or 10 mg. The blood pressure, pulse and respirations were then checked every hour for at least twenty-four hours. Six to twelve hours after the administration of reserpine an electrocardiogram was taken, and creatinine clearance* (including blood urea nitrogen determinations) was measured, in an attempt to correlate alterations in renal and cardiac function with reduction in blood pressure.

Results

Table 2 summarizes the complete data obtained. The data were subjected to statistical analysis by comparison of the significance of the difference between the means (control versus drug mean) with the use of the Student's "t" test. The blood-pressure alterations were, in addition, checked by means of binomial expansion. Fifty trials were performed, including 16 at the 2.5-mg., 25 at the 5.0-mg., and 9 at the 10.0-mg. level.

The onset of effect (Table 2) was taken as the time after administration of the drug (in hours) when the diastolic pressure with the patient supine was persistently at least 20 mm. of mercury less than the control value. The duration of effect was the time from the onset until the diastolic pressure in the supine position rose to a point less than 20 mm. of mercury below the control level. The values are recorded in the supine and upright positions as "mean blood pressure," which is the diastolic pressure plus a third of the pulse pressure. Blood-pressure levels are recorded for both the control state and the state after the injection of reserpine (drug). The control figure is the blood pressure taken just before the medication. The "drug" blood pressure is the lowest sustained reading during the twenty-four hours after administration. Some of the patients had postural syncope and, in such cases, the "mean blood pressure with the patient upright (drug)" is arbitrarily recorded as 60. Patients who were responsive were questioned for subjective symptoms. Observations were made by nurses and the investigators, and all side effects are noted in Table 2.

There were no allergic or anaphylactic reactions in the 50 trials. There was a considerable variation in the interval before onset of effect — from one to seven hours. However, there was a close grouping around the average of three hours. In most cases, there was a noticeable drop within ninety minutes. A review of our results revealed no difference in the onset of effect because of the different dosages. The duration of effect varied from two to twenty-five hours, with a mean of ten hours. Different doses did not produce any significant alteration in duration of effect.

The blood pressure decreased in all 50 trials. In 46 of the 50 trials, there was a drop of 20 or more, with a mean drop of the mean blood pressure in the supine position of 37.1 and in the upright of 46.1 mm. of mercury. These results are significant, as shown by the fact that the P value of the significance of the differences between the means is at the 99 per cent level. The possibility that these results were chance rather than drug effect were further checked by means of binomial expansion, which revealed a likelihood of chance of $1:2^{38}$ — a highly significant result.

In the determination of the hypotensive effects of reserpine, we were also interested in the quantitative dosage response. The dosage of each trial (Table 2) was analyzed in relation to the results for each dose (Table 3), — that is, 2.5, 5.0 and 10.0 mg. These results, when statistically analyzed by the Student's "t" test, were not significant. However, all patients did not receive all three dosages, and no patient received 10.0 mg. of reserpine as an initial dose. Therefore, the possibility that the group receiving 10.0 mg. was made up predominantly of patients with intractable hypertension (or more severe hypertension) may explain the apparent short duration of action, delay in onset and degree of blood-pressure reduction.

The severity of the renal disease and its effect on the hypotensive action of the reserpine was considered (Table 4). As noted in Table 2, the renal changes in each patient were graded, and the hypotensive effects of the drug in each group were compared with those in the other two groups. These three comparisons — that is, 1 and 2, 1 and 3, and 2 and 3 — gave results that were not statistically significant.

Undesirable side effects of the agents were noted. The most common side effect was somnolence, which, in this group of patients, was not particularly undesirable. It was recorded in 8 of the 50 trials, and may have been more frequent since 3 of the patients were intermittently comatose throughout their hospital stay. Nasal congestion was recorded only once, as was the onset of loose stools. The most unpleasant side effect was anxiety, noted in 4 cases and severe in 2 (both of these after 10-mg. doses). There were no complaints of nausea, vomiting or abdominal distress, and no hematologic changes were noted.

Additional observations included a determination of creatinine clearance six to twelve hours after the administration of the drug. These results are not included in Table 2. However, statistical analysis on the changes in the creatinine clearance revealed no significant change. As noted above (under "Methods

*The creatinine clearance (endogenous) determinations were done by nurses. The patient fasted for eight hours and then drank 500 ml. of distilled water. One hour later, he voided, and the urine was discarded. If he had an indwing catheter, the drainage bottle was disconnected. One hour after voiding, he again voided, and this specimen was saved. Blood for creatinine analysis was then drawn. The patient then drank 500 ml. more of distilled water and, one hour later, he again voided, and this urine was also saved. The two specimens were then analyzed for creatinine.

TABLE 2. *Response of Hypertensive Patients Receiving Reserpine Intramuscularly.*

PATIENT	DOSE	ONSET OF EFFECT	DURATION OF EFFECT	MEAN BLOOD PRESSURE WITH PATIENT SUPINE		MEAN BLOOD PRESSURE WITH PATIENT UPRIGHT		SIDE EFFECTS
				CONTROL	DRUG	CONTROL	DRUG	
	mg.	*hr.*	*hr.*					
B.C.	2.5	6	12	168	133	188	140	Nasal congestion
V.A.	2.5	1	4	170	143	160	137	
J.N.	2.5	1	10	160	97	150	93	
T.S.	2.5	3	9	167	159	123	100	
J.F.	2.5	1	5	157	132	170	153	
G.G.	2.5	4	11	183	123	167	93	Liquid stool
J.D.	2.5	3	9	177	130	167	97	
H.F.	2.5	1	35	197	117	174	103	
J.E.	2.5	1	3	153	136	137	120	Anxiety
J.E.	2.5	4	22	153	123	147	127	Anxiety
F.W.	2.5	7	9	180	133	160	120	
F.W.	2.5	4	18	205	153	197	147	
F.W.	2.5	2	8	187	147	190	149	
S.M.	2.5	6	18	197	149	167	118	Somnolence
S.M.	2.5	1	7	173	140	—	—	Somnolence
W.M.	2.5	3	25	147	89	143	67	
B.C.	5.0	0	0	190	173	—	—	
B.C.	5.0	7	30	210	153	—	—	
V.A.	5.0	4	5	173	141	157	113	
V.A.	5.0	4	11	177	130	173	130	
V.A.	5.0	1	14	177	133	143	127	
V.A.	5.0	11	12	183	147	159	130	
V.A.	5.0	4	3	180	160	183	128	
J.N.	5.0	1	3	140	113	138	103	Weakness
T.S.	5.0	3	5	167	120	123	87	
J.F.	5.0	1	18	160	133	159	103	
J.F.	5.0	1	9	160	143	150	107	
J.F.	5.0	1	10	163	153	183	118	
J.F.	5.0	3	11	183	128	173	77	
G.G.	5.0	2	8	153	112	133	103	
J.D.	5.0	1	12	177	126	167	107	
J.D.	5.0	3	8	170	123	160	100	
J.D.	5.0	4	12	170	120	150	93	
J.D.	5.0	4	9	175	130	167	117	
J.D.	5.0	2	18	177	127	144	60	
J.D.	5.0	5	7	153	112	139	60	
H.F.	5.0	0	0	160	150	153	137	
J.E.	5.0	2	10	160	133	147	120	
F.W.	5.0	0	0	171	160	163	140	
F.W.	5.0	2	16	190	138	199	130	
F.W.	5.0	2	10	203	145	188	127	
V.A.	10.0	0	0	190	178	—	—	
T.S.	10.0	4	10	153	127	120	100	
J.F.	10.0	5	2	167	130	177	136	
G.G.	10.0	4	8	153	110	127	87	
J.D.	10.0	9	7	160	130	151	93	Anxiety
H.F.	10.0	10	10	170	136	157	124	
J.E.	10.0	2	6	140	123	130	110	
F.W.	10.0	2	12	192	167	—	—	
S.M.	10.0	3	15	160	118	143	113	
Mean		3.1	10.3	171.6	134.5	157.7	111.6	

and Materials"), creatinine clearances were done on the ward by the nursing service, the urine collections were voided specimens (except for patients with in-lying catheters), and there was no bladder irrigation before the test started. A stop watch was not used, and there was no terminal bladder washout.

The results of the electrocardiograms were also not included in Table 2. There were no significant changes recorded in the tracings before and after the drug. It is worthy of note that even in the patients with the most profound hypotensive effect there was no alteration in the electrocardiogram.

Discussion

Reserpine, the most important of the *R. serpentina* alkaloids, was first isolated in Switzerland in 1952.[2] Studies in various species of laboratory animals have shown influences on the central portion of the autonomic nervous system and on the cardiovascular system, especially on the responsiveness of the reflexes that ordinarily regulate the level of the blood pressure.[3] Wilkins[4] gave the drug by mouth to young, labile, hypertensive patients and reported results

Table 3. *Summary of Response to Various Doses of Reserpine.*

Dose	No. of Trials	Decrease of Mean Blood Pressure with Patient Supine	Mean Onset of Effect	Mean Duration of Effect	Side Effects
mg.			*hr.*	*hr.*	
2.5	16	42.0	3.0	12.8	3 noted
5.0	25	33.0	2.7	9.6	1 noted
10.0	9	24.6	3.6	6.4	2 noted

superior to those using a crude powdered root (*R. serpentina*). In his series there was a delay in action of three to seven days. Using parenteral reserpine alone and in the combination with veratrum or hydralazine, Finnerty and Sites,[1] as noted above, obtained excellent results in patients with acute and severe hypertension. Hafkenschiel and Sellers,[5] who gave reserpine intravenously in an acute experiment, observed that 50 per cent of their patients showed a 20-mm. drop within the first hour; they gave as much as 4 mg. in a five-minute period, with no untoward effect. Studies by Moyer[6] revealed no consistent effect on cardiovascular and renal hemodynamics, agreeing well with our clinical findings. Hughes, Moyer and Daeschner[7] found that parenteral administration of reserpine was effective and safe in the treatment of hypertensive emergencies on a short-term basis.

Figure 1 shows the typical response. There was a smooth fall during the first three or four hours after administration followed by a slow rise over the next ten hours, the blood pressure returning to pretreatment levels thirteen to sixteen hours after administration. The results of this study confirmed many of the reported findings. The most important observations in our study were the predictable response and the expected time of onset and duration. The absence of changes in the electrocardiogram correlated with laboratory evidence of insignificant cardiovascular changes. Creatinine clearances were not significantly

Table 4. *Effects of Reserpine in Hypertensive Patients with Various Degrees of Renal Disease.*

Grade of Renal Disease*	No. of Trials	Mean Decrease in Blood Pressure	
		Supine Position	Upright Position
1	1	58.0	76.0
2	26	35.5	45.0
3	23	37.7	43.4

*See grading at bottom of table 1.

altered, and there was also no change in urinary output. The fact that renal disease had no influence on the hypotensive effect agreed with the theories of central action of the drug.

Summary and Conclusion

A predictable hypotensive response may be expected in patients with severe hypertension treated

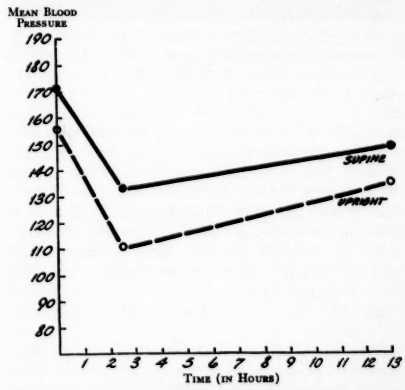

Figure 1. *Composite Effect of 2.5 Mg. of Reserpine Intramuscularly (Mean Effect in 50 Cases). Mean blood pressure = diastolic pressure plus one third of the pulse pressure.*

with reserpine by parenteral injection. A dose of 2.5 mg. administered intramuscularly was found to give a maximum hypotensive effect, rapidity of onset and duration of action, with fewer unpleasant side effects than larger dosages. The average onset of effect was three hours, the usual duration of effect being slightly more than ten hours. No statistical or clinical re-

lation between duration or severity of renal disease and response to this agent was demonstrated. Finally, the agent is a satisfactory one to use with a smooth fall in blood pressure without sudden or marked variations and with predictable results. In addition, there are few undesirable side effects.

From this study, a dose of 2.5 mg. of reserpine intramuscularly every twelve hours can be recommended as adequate for the treatment of hypertensive crises. Thus, reserpine administered intramuscularly appears to be the treatment of choice for hypertensive crises.

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EXPERIMENTAL CRYPTOCOCCOSIS PRODUCED BY THE INGESTION OF VIRULENT ORGANISMS*

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ANCON, CANAL ZONE

THE lungs are usually considered to be the primary portal of entry for the pathogenic yeastlike fungus, *Cryptococcus neoformans*. The appearance of the lungs at autopsy of human beings dying of cryptococcosis has suggested that these organs were the first to become infected. The clinical histories of many patients have offered further evidence, since symptoms of pulmonary disease have often long antedated the terminal signs of central-nervous-system involvement.[1,2] However, in some cases, lesions of the lung due to infection by these pathogenic organisms cannot be demonstrated at autopsy, despite extensive tissue involvement elsewhere. Symptoms of meningoencephalitis have frequently been the only indication of infection in some patients.[2,3] Several authors have proposed traumatic lesions of the skin or mucous membranes as the original site of entry, but the evidence of the adjudged primary focus is inconclusive.[4,5] Although the alimentary canal has generally been accepted as a possible portal of entry for these organisms, this has not been confirmed experimentally. This report deals with an attempt to produce cryptococcosis in marmoset monkeys by causing them to ingest virulent organisms.

The cryptococci used in the experiment came from a patient who had died of the disease at the Philadelphia General Hospital in 1951.[6] (This stock culture was obtained through the courtesy of Dr. Albert M. Kligman.) Generalized cryptococcosis has been produced in marmosets through the intravenous inoculation of this particular strain.[7]

Methods

The marmoset monkeys, *Leontocebus geoffroyi* (Pucheran), were purchased from animal dealers in the Republic of Panama. They were recently captured wild monkeys. Each was tested by one or more blood cultures to rule out the possibility of a spontaneously acquired infection. The pathogenic yeasts were introduced into the digestive tube by feeding of banana sandwiches made with a filler of cryptococci. This filling was prepared by mashing of fragments of banana into a paste with a dense physiologic saline suspension of the yeasts. This paste was placed in hollowed areas between two thin slices of banana, which the monkeys readily ate. The sandwiches were followed by segments of clean fruit. Organisms from the original stock culture of the yeasts were used in the experiment. The number of the yeasts in the saline suspension was determined by the use of a hemocytometer. A control marmoset was fed a sandwich prepared from the same banana used with the experimental monkeys, but in this case the filler contained mashed banana and saline suspension without the yeasts.

The marmosets, both experimental and control, were kept in separate small cages in a small-animal room. All were fed on a diet of native fruits, bread and small portions of cooked meats. Each animal was given multivitamin drops in its food at least twice a week.

The infections were permitted to run their natural course; no medication was given. Each animal was completely and promptly autopsied after death. Two tissue blocks were taken from each organ for the preparation of histologic sections. Seven such blocks were usually taken from the brain, and at least three from the spinal cord.

Cultures were run on Sabouraud's glucose agar routinely with material taken from the brain, spinal cord, liver, lungs, spleen, kidneys, oral pharynx, esophagus, stomach, small and large intestine, cecum and

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sigmoid colon. Every effort was made to eliminate the possibility of carrying the yeasts from an infected to an uninfected organ. Material from the brain and lungs was cultured on blood agar in addition to the routine Sabouraud medium.

Results

All 3 monkeys subjected to the experiment were ill the day after they ingested the sandwiches containing cryptococci. They became dull and apathetic and refused to eat. The control monkey never became ill at any time. One marmoset, A-6, which had ingested 54,000,000 yeast organisms, died on the fourth day. The others (A-5 and A-7) recovered spontaneously in about a week and became active, hungry and apparently healthy. They remained symptom free until three days before they died, when signs of central-nervous-system disease were first observed. At first the marmosets were highly irritable, and fine tremors could be seen in the muscles of the extremities. Later, there was a gradually spreading paralysis and a tendency to opisthotonos. These symptoms were exactly like those seen in the same type of marmosets infected intravenously with the same strain of cryptococci.[7] Monkey A-5, which had eaten 108,000,000 yeast organisms, survived for nineteen days; A-7 lived for thirty-two days after ingesting 150,000,000 organisms. Table 1 summarizes the details regarding these animals.

At autopsy one lesion was common to the marmosets subjected to the experiment: the small intestines were markedly distended. In monkey A-6 there was an extensive paralytic ileus involving practically the entire small bowel from the duodenal flexure to the ileocecal valve. There was a more segmentally distended small bowel in the marmosets surviving for more than four days, large areas of apparently normal intestine occurring between the distended loops. The dilated bowel contained a viscid, greenish fluid, within which large gas bubbles were trapped. The mucosa of the small bowel appeared to be normal on gross examination, as did the lining of the rest of the alimentary tract. No abnormality, other than the distended small bowel, was seen on gross examination.

Table 1. *Survival Time of Marmosets Ingesting* C. neoformans.

Monkey No.	Sex	Weight	Number of Organisms Ingested		Survival Period
			Total in millions	Thousands per gram of marmoset	
		gm.			*days*
A-6	Male	350	54	154	4
A-5	Male	280	108	385	19
A-7	Male*	195	150	769	32
A-4C	Male†	290	None	None	180‡

*Immature.
†Control.
‡At time animal was killed.

Microscopical examination of numerous histologic sections prepared from all parts of the alimentary tract failed to reveal lesions of cryptococcosis. Even the sections taken from the most distended portions of the small bowel did not give evidence that the fungi had invaded the mucosa. A thick coating of mucus covered the intact mucosa of the small intestine, and there was no evidence of inflammatory exudate. Lesions of cryptococcosis were not found in the tissue sections prepared from the organs of the marmoset (A-6) that died four days after eating the fungi. In the monkey surviving for nineteen days, a single lesion containing many of the parasitic yeast organisms was found in a mesenteric lymph node. Histologic sections from other parts of this animal did not reveal any disease. The marmoset that survived for thirty-two days (A-7) had focal involvement of the brain and myocardium (Fig. 1 and 2), as well as extensive involvement of the mesenteric lymph nodes. Neither yeast organisms nor lesions were found in any of the sections from the lungs, liver, spleen, stomach, oral pharynx, small and large intestines, testes, suprarenal glands and kidneys. Many of the sections, especially those from the small bowel, were stained by the Hotchkiss–McManus fungous stain technic as well as by the standard hematoxylin and eosin method.

Figure 1. *Portion of a Lesion of the Myocardium of Monkey A-7, Showing Yeast Organisms (Hematoxylin and Eosin Stain X 430).*

Cultures taken from the stomach, small and large intestine and cecum grew colonies of cryptococci. This was true in all animals fed the organisms. Al-

though it was attempted to culture only the mucosal wall of the digestive tube, contamination by the contents of the lumen was inevitable. The fungi were cultured only from the digestive tract of monkey A-6; all the other tissues were sterile. The meninges, liver and spleen of the marmoset living for nineteen days (A-5) yielded pure cultures of cryptococci. However, the yeast organisms could not be grown from the brain substance itself. The brain, liver, spleen and

FIGURE 2. *Section of the Brain of Monkey A-7, Showing Characteristic Lesion of Cryptococcosis (Hematoxylin and Eosin Stain X 190).*

spinal cord of marmoset A-7 yielded pure cultures of the pathogenic yeast organisms. Every culture attempted from the lungs, kidneys, oral pharynx and esophagus failed to show any growth.

To be certain that cryptococci had been isolated, material from each culture that showed growth was studied microscopically. A further check was run on all the organisms isolated from the large bowel to be sure that these were pathogenic strains of the yeasts. Cryptococci were subcultured on Sabouraud's medium from the colonies originally isolated from the monkeys. These were suspended in physiologic saline solution, and 25,000,000 organisms were injected intraperitoneally into white rats. One rat was used for each culture. The rats died in three to fifteen days, and lesions of cryptococcosis were found in the tissue sections of each of the three rodents used.

None of the monkeys gave evidence of helminthic infections of the bowel on gross or histologic examination. The control marmoset was maintained for six months without the development of any sign of illness. It was killed at that time and autopsied in the same manner as the other animals. Neither tissue sections nor cultures yielded any evidence of infection with cryptococci.

DISCUSSION

In 2 of 3 marmosets systemic infections with *C. neoformans* followed the ingestion of a pathogenic strain of these yeastlike fungi. Lesions of cryptococcosis were found in sections of the brain and heart as well as the mesenteric lymph nodes of an animal surviving for thirty-two days. A single microscopical lesion involving a mesenteric lymph node was found in a monkey dying nineteen days after ingesting cryptococci, but organisms were isolated in pure culture from the meninges, liver and spleen. If this animal had survived a few weeks longer, there is little doubt that further tissue lesions would have developed. In the monkey that died after four days, the yeasts could be obtained from the digestive tract only; all other tissues from this marmoset failed to yield cultures of cryptococci. The animal that received the greatest number of yeast organisms survived the longest. This was a young, subadult monkey, whereas the others were mature adults.

Nothing was found to indicate how the fungi passed from the lumen of the alimentary tract into the body tissues. No lesions of the mucosa were demonstrated either grossly or microscopically. The mesenteric-lymph-node involvement found in the animals that survived the period of acute illness suggests that the yeast organisms somehow entered the lymphatic drainage of the bowel. The ileus noted at autopsy may have produced conditions that enabled the cryptococci to pass through the apparently intact mucosa. Once in the lymphatics, the fungi invaded the mesenteric lymph nodes and caused the destruction of the usual nodal architecture. From these lymph nodes, they could gain access to the blood stream either directly by the erosion of a vessel involved in the lesions or by way of the lymphatic duct. Once in the blood stream, they were distributed to all parts of the body.

The present study indicates that cryptococci can survive passage through the gastric juices and succus entericus of the marmoset. Apparently, such passage does not decrease the pathogenic properties of these yeasts. Indeed, they can live in the digestive tract for several weeks without affecting their virulence for white rats.

Nonpathogenic strains of these yeasts have been isolated from the skin and bowel of normal human subjects. Some of these nonvirulent forms have produced lesions when injected into vitamin-deficient rats.[8] Cultures made from the digestive tract at autopsy of patients dying from diseases other than cryptococcosis have yielded strains of *C. neoformans*.[9] Apparently, it is not unusual for these organisms to be ingested in nature.

Lesions have been produced in many types of lab-

oratory animals by nearly every method by which injections can be made, but there are very few records of attempts to introduce infection via the natural portals of entry. Wade and Stevenson[10] infected a white mouse by introducing the yeast organisms into the trachea; this animal showed lesions of the lungs and kidney when it died after thirty days. A second mouse, similarly infected, lived for a hundred and twenty days, and no lesions were found when it was killed. An attempt to infect a Rhesus monkey by way of the lungs did not succeed.[11] Pounden et al.[12] recently attempted to infect a ten-week-old calf by feeding it 200 ml. of a broth culture of cryptococci. No evidence of infection could be found either in the tissues or by cultures when the calf was killed after thirty-seven days. This calf had also received 0.5 ml. of the same culture intravenously and subcutaneously.

From the present study it is evident that infection can take place by way of the digestive tract of the highly susceptible marmoset. It is realized that massive doses were used, but it was desired to produce acute rather than extended infections. Since the cryptococci are widely distributed in nature and have been isolated from time to time from the human digestive tract, it seems obvious that infection by mouth may present a real danger. Virulent strains of these yeasts have been isolated from fruit skins[2] and raw milk,[12,13] so that infection might take place in human beings through the ingestion of foods containing pathogenic strains of this yeast. There can be little doubt that the digestive tract may represent an important portal of entry of these organisms.

Summary

Systemic cryptococcosis was produced experimentally in 2 out of 3 marmoset monkeys through the oral portal of entry by ingestion of virulent *Cryptococcus neoformans*. These yeasts retained their pathogenicity for white rats after several weeks in the marmoset intestine. Evidence is presented that the digestive tract may represent an important portal of entry for these pathogenic yeast organisms.

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SUCCESSFUL REMOVAL OF A MYXOMA FROM THE LEFT ATRIUM*

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BOSTON

We are reporting herewith the surgical removal of a myxoma from the cavity of the left atrium. The procedure was carried out under hypothermia and represents the first successful case reported from this country and the third in the literature (Crafoord,[1] in 1954, and Bigelow et al.,[2] in 1955, having recorded previous cases).

The presenting symptoms and signs, as is usual, were characteristic of mitral stenosis of high degree. This is important, for it is certain that as an increasing number of intracardiac operations are carried out greater numbers of tumors primary within the chambers of the heart will be recognized. To our knowledge at least 8 unsuccessful attempts to remove intra-atrial myxomas have been made during the past five years.[3-6]

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Case Report

L.W. (M.G.H. 655597), a 33-year-old construction foreman, entered the hospital on March 9, 1955, because of dyspnea and hemoptysis. The past history was negative for rheumatic fever and chorea, and he had always led a vigorous and active life. In 1949 he had been examined at the Massachusetts Eye and Ear Infirmary for iritis secondary to a foreign body, and no cardiac abnormalities had been noted.

Eighteen months before entry he had a "cold" followed by cough, dyspnea, asthmatic breathing and a small hemoptysis with streaking of the sputum for several days. His physician found a slight cardiac murmur and prescribed treatment for asthma. In another week he was well and returned to his active job free of symptoms.

Twelve months later he had a 2d unexplained episode of acute dyspnea and slight hemoptysis twice. An injection relieved the dyspnea.

Thereafter, he was well until 1 month before entry, when a cough developed. A week later hemoptysis occurred, in-

creasing to several tablespoonfuls a day, with persistent and slowly progressive dyspnea, wheezing and orthopnea. He entered the hospital for "study of his lungs."

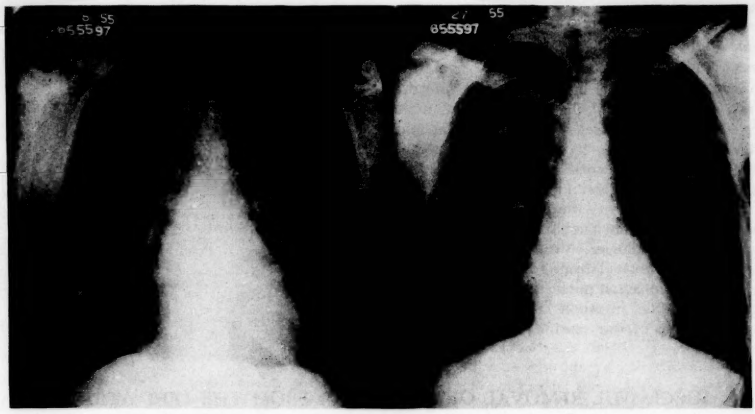
Physical examination revealed a healthy-appearing man who was dyspneic at rest. There were a few rales at the right-lung base, but no congestion of the cervical veins or of the liver and no edema. Examination of the heart showed the classic signs of pure mitral stenosis. There was slight enlargement, and the rhythm was regular. At the cardiac apex there was a typical presystolic roll of Grade-3 intensity, ending with crescendo in a sharply accentuated 1st sound. There was an associated presystolic thrill. The pulmonic 2d sound was moderately loud, and there was an opening snap. No systolic murmurs were detected. The blood pressure was 90/55.

An electrocardiogram showed the pattern of right ventricular hypertrophy and prominent, broad P waves consistent with hypertrophy of the left atrium.

Under the existing circumstances — particularly since we were aware of the disasters that had inevitably occurred when *impromptu* attempts to remove such tumors had been made — it was thought best to postpone removal until, under hypothermia, the circulation could be interrupted temporarily, the left atrium opened and the tumor excised deliberately. The atrial appendage was closed, therefore, saving as much length as possible, and the operation terminated.

The patient had an uneventful course after this procedure. The left lung re-expanded well, and the cardiovascular status remained good. Preparations for a 2d procedure were made.

At the 2d operation, carried out on June 15, the patient was given Pentothal intravenously in his room at 7:05 a.m. and then transferred to the operating room, where, after topical cocaine anesthesia, an intratracheal tube was introduced. Anesthesia was then continued with Pentothal and



A B

FIGURE 1. *Roentgenograms of the Chest.*

The preoperative film (A) *shows slight cardiac enlargement, with fullness of the left atrium and congestion of the lung roots. The postoperative film, taken six weeks after operation* (B), *shows the heart to be somewhat smaller and the lung roots to be normal.*

X-ray study disclosed a slightly enlarged, triangular-shaped heart, with fullness of the left atrium and congestion of the lung roots (Fig. 1).

Laboratory studies gave no evidence of infection. A modest diuresis occurred with Mercuhydrin; the pulmonary congestion cleared, and the dyspnea and hemoptysis promptly subsided. The patient was considered to have uncomplicated pure mitral stenosis of high degree, and in view of the recent and alarming increase in his pulmonary symptoms, a commissurotomy at an early date was advised. For personal reasons he was allowed to go home while arrangements for operation were completed. He returned on May 17.

At the first operation, which was carried out on May 23 under intratracheal nitrous oxide, oxygen and ether anesthesia, a posterolateral approach was used. The atrial appendage was of normal size and configuration, providing easy entry into the atrium, which the exploring finger showed to contain a soft, lemon-sized mass attached by a narrow pedicle to the base of the interatrial septum close to the posteromedial commissure of the mitral valve (Fig. 2). The valve itself was of normal size and consistence. Palpation of the valve, however, was made difficult because part of the tumor mass had prolapsed into the valve orifice, effectively interfering with blood flow through that structure. There was a minimal degree of mitral regurgitation.

curare as needed to control shivering. Cooling was effected by the surface application of ice packs. The body temperature was monitored by an intrarectal and an esophageal recording thermometer. The body temperature gradually fell from 37.0°C. (98.6°F.) to 29.7°C. (84.2°F.) in approximately 3 hours (Fig. 3). At this point, the ice packs were removed, and operation begun. As had been anticipated, the body temperature continued to drift to 27.2°C. (81°F.) during the 45 minutes that were found necessary to reopen the chest incision and control the vessels leading to and from the heart.

An anterolateral approach was used. The previous incision was extended forward in the 4th interspace to the edge of the sternum, which was transected at this level, and the incision continued into the 4th interspace on the right. This provided adequate exposure for the problem at hand. Traction tapes were then placed about the right innominate and left common carotid arteries. The pericardium was opened widely, and the atrial appendage freed from loose inflammatory adhesions. The pericardial incision was extended across the anterior surface of the heart, and the superior vena cava identified and isolated. The inferior vena cava was also identified, and although it could not readily be dissected free, it could easily be occluded by a noncrushing clamp. It was determined that the transverse

sinus of the pericardium was patent so that it would be possible to crossclamp the aorta and pulmonary artery and in this way to interrupt the flow of blood to the lung *after* the venous return to the heart had been interrupted.

After these preliminaries, the atrial appendage was reopened, and the presence of a tumor confirmed. As before, it seemed to arise from the base of the interatrial septum, but on this occasion the mass did not prolapse into the mitral orifice but lay free in the atrium. (In this connection it is interesting that on the eve of operation the patient had been examined by the cardiac resident, who made a note that he was unable to hear the apical diastolic murmur that had been clearly evident to all previous examiners.)

Removal of the tumor was then carried out in the following manner: both internal carotid arteries were occluded by serrefine clamps; a Crafoord clamp was placed across the inferior vena cava; the superior vena cava was occluded by traction on a previously placed tape; the aorta and pulmonary artery were crossclamped with a Crafoord clamp; and the atrium was opened by extension of the atrial incision. Only a very moderate amount of blood escaped. The edges of the atrial incision were retracted, and the narrow stalk of the somewhat lobulated tumor separated by finger dissection from the atrial septum; the tumor was then delivered through the incision by means of a modified prostatic-lobe forceps. With the tumor removed, the interior of the atrial cavity was inspected. It was relatively bloodless, and no residual tumor could be identified. The atrial and ventricular cavities were then filled with saline solution to prevent peripheral air embolism, and the atrial incision grasped in a curved Potts clamp.

The cardiac action, which up to this point had been good, although the pulse was slow, now suddenly changed to

FIGURE 2. *Photograph of the Tumor Removed from the Atrium.*

The groove made by pressure of the mitral ring is well seen. The portion of the tumor that had prolapsed into the ventricle is to the left.

ventricular fibrillation. The atrial incision was rapidly oversewn, and the occluding clamps were removed in the reverse order to which they had been applied. The time of total interruption of the circulation was 5½ minutes.

With the clamps removed an effort to defibrillate and resuscitate the heart was begun. Manual compression and release of the heart ("massage") was effective in restoring a recordable peripheral pulse pressure of 60/40. Even with this perfusion of the myocardium, repeated attempts to resuscitate the ventricle after electric defibrillation were unsuccessful. After each shock, the ventricle ceased to beat. When it failed to develop a normal rhythm, the reinstitution of cardiac massage invariably led to resumption of ventricular fibrillation. On several occasions 2 or 3 ml. of dilute epinephrine (5 microgm. per milliliter) and 5 ml. of a 1 per cent solution of calcium chloride were injected into the left ventricle, but without the desired response.

At this point the body temperature had fallen to what we interpreted to be the critically low level of 26.4°C. (79.5°F.). To rewarm the heart, therefore, the pericardium and chest cavity were flooded with large amounts of warm — 40°C. (104°F.) — saline solution. The rise in body temperature was distressingly slow. Throughout this period, however, a measurable peripheral pulse was maintained, interrupted by short periods of attempts to defibrillate by electric shock. After 1 hour, when the body temperature was still 26.8°C. (80.2°F.), the heart reverted to idioventricular rhythm for about 10 minutes and then reverted to ventricular fibrillation. One hour later, or 2 hours after the onset of fibrillation, the body temperature had reached

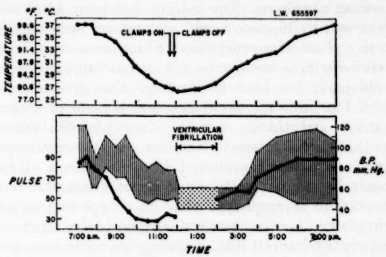


FIGURE 3. *Chart of the Body Temperature, Pulse and Blood Pressure during the Course of Anesthesia, Operation and Recovery.*

The surface packs were removed and operation begun at 10 a.m., approximately halfway along the descending portion of the temperature curve.

27.5°C. (81.5°F.), and a 2d reversion to normal sinus rhythm occurred after electric shock and the intraventricular injection of calcium chloride.

When it became evident that regular rhythm had been re-established, the pericardial and chest incisions were closed. The patient was wrapped in warming blankets, and the body temperature gradually rose, reaching 37°C. (98.6°F.) by 8:00 p.m. — 12½ hours after cooling had begun. At that time he was oriented, and the pulse and blood pressure were well maintained at 88 and 105/45 respectively.

The remainder of the postoperative course was remarkably benign. After rising to 100 during the first 48 hours, the pulse was steadily in the range of 80 to 90. On the 14th postoperative day a transient rise in temperature, pulse and respirations combined with a small hemoptysis raised a serious suspicion of pulmonary embolism, and Dicumarol was started. The patient was kept in bed for 2 weeks postoperatively out of deference to his myocardium, which had of necessity been traumatized by prolonged massage. He was discharged to convalescent care on the 24th postoperative day. Progress thereafter was entirely satisfactory. He returned to work as a steel-construction worker 5 months after operation.

The final pathological report on the tumor removed was myxoma, presumably benign.

DISCUSSION

The clinical picture presented by this patient was indistinguishable from mitral stenosis. Although it is possible to make a preoperative diagnosis of intra-atrial tumor and to confirm it by angiocardiography, as Steinberg et al.[4] have shown, almost certainly the majority of such diagnoses will be made at the op-

erating table. We are convinced that under these circumstances the surgeon will be well advised to postpone removal of the tumor until he is in a position to do so under direct vision with the circulation temporarily interrupted. At the moment, hypothermia appears to be the most convenient method of achieving this end, but it may well be that total by-pass of the heart with the use of some form of pump oxygenator will be the method of choice in the future.

Details concerning the various methods of inducing and managing hypothermia are best left for discussion elsewhere. The subject has been admirably reviewed by Bigelow et al.[7] and others[8] and is in an active phase of investigation. In our own experience, relatively slow cooling by the surface application of cold packs has been satisfactory. Our greatest concern has been the avoidance and control of serious cardiac arrhythmias, notably ventricular fibrillation, as this case illustrates. Here, the central nervous system was partially protected from the effects of hypoxia by the circumstance of hypothermia; yet it is important to emphasize that an adequate cerebral circulation was maintained manually for approximately two hours. Cardiac massage or, more accurately, manual systole, cannot be considered adequate unless it produces a palpable peripheral pulse — in this case recorded in the radial artery at 60 systolic, 40 diastolic.

Summary

The successful removal of a myxoma from within the left atrium is reported.

The management of prolonged "cardiac arrest" due to ventricular fibrillation, with eventual return to normal rhythm, is described.

The value of hypothermia as an adjunct to cardiac surgery is illustrated.

We are indebted to Drs. Hermes C. Grillo and David B. Sheldon, formerly surgical residents, for their assistance.

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MEDICAL PROGRESS

APNEA AND RESPIRATORY DISTRESS IN THE NEWBORN INFANT (Continued)*

Physiologic Background, Resuscitation and Supportive Technics

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BOSTON

Specific Technics of Resuscitation and Artificial Respiration

As indicated in the preceding discussion, technics for aiding respiration should be considered according to whether they are methods for initiating breathing, methods for supplementing the infant's own efforts during respiratory distress or methods for preventing the development of such respiratory distress. Obviously, there is considerable overlap between these three general approaches to therapy. The following two sections deal in detail with the individual methods, their theoretical applicability, their practicality and, where available, critical data on actual use. It will be apparent that there are multiple difficulties in such an evaluation and that most of the technics discussed have, at best, limited areas of usefulness. It should be kept in mind throughout that, although the ultimate aim should obviously be prevention, resuscitation at present is primarily limited to attempts to improve the responsiveness of the respiratory center and to improve and maintain the uptake of oxygen and the excretion of carbon dioxide.

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Management of Airway

Effective ventilation can only be accomplished via unobstructed air passages. Certainly, there is general agreement that removal of amniotic fluid and mucus from the nose and pharynx of the newborn infant is helpful and harmless. However, opinion continues to be divided between those who believe that the advantages of laryngeal or tracheal aspiration outweigh the dangers and trauma of instrumentation[43] and those who consider postural drainage and gentle catheterization of nasal passages and pharynx equally valuable and somewhat less dangerous.[44] There seems to be no general acceptance of routine laryngoscopy after certain types of delivery, as was once proposed for cesarean section,[45] and no justification for such a radical approach. Since recent roentgenologic studies in the newborn period indicate the rarity of local atelectasis,[46] the laryngologist will probably be less frequently asked to look for local obstruction. Moreover, as Holinger[47] recently said, "while the more frequent consultation with the laryngologist in regard to newborn infants is a request to aspirate obstructing secretions, it is almost axiomatic that, if obstruction is severe enough or secretions copious enough to necessitate this consultation, some underlying congenital abnormality or birth injury is the basic pathology responsible for the infant's condition and not the secretions themselves."

In contrast to the drastic and potentially harmful methods occasionally proposed for the management of the air passages, the simple oral airway used frequently by anesthetists may be useful in the apneic, depressed or hypotonic infant. Particularly in these infants the tongue may partially or completely occlude the pharynx and make the application of oxygen, with or without positive pressure, inefficient or impossible if some sort of airway is not used.

Drugs

Many drugs have been used in an attempt to stimulate respiration in apneic or hypopneic newborn infants. Unfortunately, only when the increasingly rare case of narcosis due to morphine or morphine-like compounds occurs is a specific agent available.

N-allylnormorphine. N-allylnormorphine (or nalorphine) hydrochloride (Nalline), a morphine derivative, apparently has a place in the treatment of an infant with respiratory depression resulting from maternal analgesia with opiates or related synthetic analgesics, including the most commonly used preparations (morphine, codeine, Demerol, Pantopon, Dilaudid, Metopon, Nisentil and heroin).[48] It is not effective in combating depression from anesthetic gases, barbiturates or other causes and is, in fact, itself a respiratory depressant when given alone.[49-53]

In spite of evidence that nalorphine may be effective in reducing depression of the infant when administered to the narcotized mother just before delivery,[50,52,54,55] most authors feel that it is best given into the umbilical vein of the narcotized newborn infant (0.1 to 0.4 mg. diluted to 2.0 ml.) after depression from birth trauma, anoxia, barbiturates or inhalation gases has been excluded.[48,52,54,56,57] If an instantaneous effect is not necessary and if the circulatory status is satisfactory, nalorphine may be given intramuscularly. The effect should then be apparent within approximately three minutes and maximal in six minutes. Repeated administration is probably without benefit and may be harmful.

When it is used for specific therapy, many pediatricians, obstetricians and anesthetists have the impression that nalorphine injection results in improved responsiveness of the narcotized infant, but the various series of cases reported provide only suggestive evidence and not proof of its efficacy.[54,56,58] Finally, although nalorphine is probably a useful preparation in the treatment of apnea caused by a specific group of drugs, good obstetric practices should almost eliminate the need for its use. Prevention of this type of respiratory depression, rather than therapy, should be the primary aim.

Other respiratory stimulants. Of the many respiratory stimulants that have been reported for treatment of the apneic newborn infant, almost all are less widely used now than previously.[59] Apnea usually occurs because of central-nervous-system depression rather than because of lack of stimulation. Lim and Snyder[60] concluded, from their study of the effects of alphalobeline, Coramine, caffeine, Metrazol and cyanide on the breathing of newborn rabbits, that none of these drugs had a place in resuscitation. Eastman and Kreiselman[61] were also unable to demonstrate any effect of Coramine, alphalobeline, or Metrazol in experimentally anoxic animals though respiration could be restored by oxygen after failure of these drugs. Thus, oxygen may be the most potent, since it is the most physiologic, stimulant to the severely anoxic respiratory center. Possibly, however, caffeine (25 to 50 mg. intramuscularly), epinephrine (0.1 to 0.2 ml. of 1:1000 solution) or other circulatory stimulants sometimes improve the cerebral circulation and relieve the depression of the apneic or hypopneic infant.

Positive-Pressure Devices

Expansion of anectatic or atelectatic lungs and oxygenation of the blood (and brain) by way of the functional lung tissue are two of the principal aims of resuscitation. For this purpose a number of methods have been devised for the introduction of air, oxygen or mixtures of the two into the lungs under pressure.

Endotracheal intubation and positive pressure. Any gas administered by positive pressure via a face mask almost invariably distends the stomach and bowel. This must cause both a delay in pressure build-up and a limitation of diaphragmatic move-

ment. Since most methods of delivering positive pressure may be adapted to either a mask or an endotracheal tube, any discussion of pressure-resuscitating technics should begin with a brief consideration of the site of application.

Full-term or premature infants may be safely intubated by an experienced operator, and the tube left in place for one or two hours.[62] A tracheal tube should be short enough (approximately 12 cm.) to obviate the danger of passage to the carina with obstruction of one main bronchus and overloading of the other lung. The tube (diameter of approximately 3 or 4 mm.) must occlude the trachea to avoid leakage and yet not produce significant trauma. Some workers prefer to use a narrower tube, which allows flow of oxygen into the trachea and escape to the pharynx, but their purpose is not lung inflation under pressure.[63]

Although a trained operator can safely place a snug-fitting endotracheal tube in a newborn infant, the procedure should certainly not be a routine one. Its use would be advisable—if ever—when simpler measures have failed and when a device is available for the delivery of gases under pressures known to be both safe and effective. Under these ideal circumstances application of positive pressure to the trachea will probably be more effective than when only a mask is used, but it must be remembered that the increased effectiveness is achieved only at the expense of increased need for careful pressure and volume control. As will be clear from the following discussion, the greatest present handicap in the use of positive-pressure resuscitation is the lack of agreement on how much pressure thus applied is both safe and effective.

Simple positive pressure. Mechanical devices for giving oxygen or some mixture of gases to infants with apnea usually provide a built-in safety valve preventing pressures above certain levels. Representative of this class is the machine introduced by Kreiselman[64] in which mask pressures can be adjusted so as not to exceed an upper limit that may be selected by the operator at between 1 and 22 cm. of water (1 to 16 mm. of mercury). The operator closes and opens a valve on the mask to produce the build-up and release of pressure. Obviously, the rate of build-up will depend in part on the flow of oxygen, a factor that cannot be properly controlled. The highest mask pressure of this machine is presumably without danger to the infant's lungs, but has recently been criticized as being below that necessary to inflate the lungs of some stillborn infants in vitro.[37]

Although it is unlikely that a sudden increase in mask pressure to 22 cm. of water would send a pressure wave of this magnitude down the trachea and out the bronchi and bronchioles, some expansion of the lungs should occur in most infants in whom pulmonary surface tension and resistance of the chest itself are relatively normal. But in infants with lungs with increased flow resistance or reduced compliance, prompt effective artificial inflation is unlikely. It is more probable that scattered areas of greater compliance are selectively inflated and the process may spread to include other segments. The apneic infant's color commonly improves, and he usually begins to breathe for himself. Whether he would do so without this artificial procedure is never absolutely known, but at least oxygen is much more readily available to the lungs of the infant when he takes his first gasps. Such an apparatus probably acts more as a safe aid to the apneic infant in resuscitating himself than as a direct cause of pulmonary ventilation.

Positive-negative pressures. Appliances of the positive-negative-pressure type are used both for initiating respiration and for subsequent short-term aid. The commercially available machines, such as the infant resuscitators of the Emerson and E and J types, cycle between +18 and −12 cm. of water,[65] and will not supply oxygen at any greater pressure if the need arises in a particular case.[66] Once the oxygen valve is set, the duration of each cycle is determined by the length of time it takes to build up to these critical pressures within the mask-patient system. The factors involved here are as follows: lung and thorax compliance; resistive forces in the air passages (including frank obstruction); and the rate of flow from the machine. An increased flow rate through the air passages will increase the resistive forces and shorten the cycle enough to decrease the tidal volume.[67] One may interrupt the cycle without altering the duration of the positive pressure by removing the mask momentarily after each negative phase. However, it is impractical to synchronize the positive-pressure phase with any spontaneous inspiratory efforts on the part of the infant. Whenever the spontaneous breathing becomes adequate, the machine can be switched to simple inhalation oxygen.

Theoretically, the negative pressure might improve venous return and cardiac output or, conversely, increase surface-tension factors undesirably. Whittenberger[67,68] has reviewed this problem and concluded that, in most of the commercially available machines, the negative phase is not of sufficient magnitude to have either of these effects to a significant degree. In the hands of those experienced with its use, the appliance is apparently as safe and as effective as the hand-controlled intermittent positive pressure supplied by the Kreiselman type of apparatus.[69,70] No studies have been found by which the added feature of negative pressure in the resuscitation of apneic infants can be further evaluated.

Short, higher pressures. Certain infants, at or shortly after birth, may have lungs that are abnormally resistant to adequate inflation. The cause of this phenomenon, which appears to be one aspect of the respiratory-distress syndrome, is unknown, but seems to be something more than the usual cohesion of wet surfaces.[33] In any event, certain areas of the

lungs of such infants may be ruptured by positive pressures of 20 to 25 cm. of water without the simultaneous occurrence of adequate generalized expansion.[71] This dilemma has led to studies, particularly by Day and his co-workers,[37] of the effects of much higher pressures exerted over shorter periods. Investigations of time-pressure relations in the inflation of excised lungs of animals of various species showed that even low pressures, in the range of conventional resuscitators, could cause overdistention and consequent damage when their duration was not restricted. With pressures up to 25 cm. of water, unaerated alveoli failed to expand, whereas aerated alveoli distended to the point of rupture. When the duration was limited to 0.15 second, however, the higher pressure of 40 cm. of water inflated both atelectatic and nonatelectatic excised lungs without injury. The timing was critical; an increase to 0.2 second caused alveolar damage at the same pressure. When the application of these data are considered, it should be remembered that most of the information applies to excised lungs. Presumably, less lung damage would occur at higher pressures in the intact organism; this fact obviously needs to be definitely established. Day[72] has suggested that air or oxygen under positive pressure of 40 cm. of water for some such brief period might safely and effectively be utilized in human infants but has not presented further studies.

An adaptation of the Day principle to babies is described by Cherniak and Boyd,[73] who used an experimental apparatus to deliver 0.1-second bursts of oxygen at a maximum pressure of 40 cm. of water. In infants with specific signs of anoxia 60 seconds after birth, an endotracheal tube was passed. A sequence of resuscitative technics was attempted, culminating, if necessary, in the use of this apparatus to deliver oxygen directly to the trachea. There was no roentgenologic evidence of lung damage in the 5 babies who survived. In the 2 who died, autopsy showed no lung injury. Final evaluation must await the accumulation of a larger series.

The resuscitator described by Goddard et al.[74,75] is an instrument in which brief, high pressures are supplied by manual compression of a rubber bulb. It may be used with a mask or endotracheal tube, and in an emergency can utilize room air until oxygen is available. Mask pressure is adjustable up to 60 cm. of water and may be reduced after initial expansion is considered to have occurred. However, the duration of pressure, which is supposed to be between 0.2 and 0.4 second, is determined by the rate and completeness of squeezing the rubber bulb, requiring practice with a model rubber-lung assembly. Further clinical trials are necessary to evaluate the safety and effectiveness of the appliance in initial inflation of the lungs. If such trials definitely establish these factors, quick-acting high-pressure devices might be tried in the prophylaxis (or treatment) of later respiratory distress as well as apnea. The greatest need at present is proof of safety. In the persistently apneic newborn infant an element of risk is justified, but if a device is to be used for prophylaxis of later respiratory distress, it must be applied to many infants who need no treatment if the occasional one who does is to be included.

Patient-cycled positive pressure. One of the difficulties in administering any form of intermittent positive pressure to a hypopneic infant is to time the pressures to coincide with feeble and irregular spontaneous respirations. Donald[58] has devised an apparatus consisting of a mask connected to a source of air or oxygen under pressure that is actuated instantaneously by the patient's slightest inspiratory effort. When the mask pressure reaches a preset figure (usually 15 cm. of water), flow is cut off and exhaust permitted. A refractory period (approximately 1.0 second) occurs after each "triggering" so that unnecessary and irrelevant triggering does not occur. In addition, a timing mechanism is built into the circuit so that if the preset mask pressure is not attained, flow is cut off, and expiration allowed. If the patient is completely apneic, the apparatus may be operated manually as a simple positive-pressure resuscitator. The duration and volume of each lung expansion depend, as with the E and J type of resuscitator, on many factors including the compliance and resistance of the lungs and thorax. In the treatment of 25 cases, no harmful effects were produced, and the results indicated a temporary benefit. However, the exact role of such an apparatus in neonatal resuscitation is not yet known. One would expect a mask pressure of 15 cm. of water to be definitely effective only in the probably rare cases in which resistance and compliance factors did not make a higher pressure mandatory for adequate pulmonary ventilation.

Mouth-to-mouth resuscitation. Since mouth-to-mouth resuscitation introduces certain obvious hazards, a number of devices placed between the patient and the operator have been designed to filter out contaminating bacteria, to prevent the application of dangerous pressure or to allow oxygen to be added to the insufflated air. This type of relatively uncontrolled insufflation probably results in too small, too large or too prolonged pressure. Elam, Brown and Elder,[76] on the basis of work in adults, believe that the human operator can sense changes in resistance and compliance and thus apply pressure as needed, but it has not been demonstrated that this is possible in infants. Actually, no convincing evidence regarding the efficacy or safety of mouth-to-mouth resuscitation in the apneic or hypopneic infant is available. That the introduction of a severe respiratory infection in the infant is a real danger has recently been re-emphasized by Penner and McInnis,[77] who were able to culture identical organisms from the oropharynx of a person administering mouth-to-mouth resuscitation and from the

lungs of the infant examined post mortem. Unfortunately, few data are available concerning the value of filtering expired air through cotton or gauze. Certainly, this form of resuscitation appears to be considerably more dangerous and less effective than the mechanical devices for applying positive pressure and should only be used when positive pressure is absolutely necessary and cannot be provided otherwise.

Oxygen

General considerations. Although added oxygen is obviously desirable in the treatment and prevention of anoxia, its use in support of newborn and especially premature infants needs reappraisal. The demonstration that retrolental fibroplasia occurs in premature infants in direct relation to oxygen administration[78] has ended the practice of unnecessary or "prophylactic" administration of oxygen. But no information is yet available about the danger—if any—from administration of oxygen therapeutically to infants who would be cyanotic or depressed without it. We believe that such a use is proper, provided the demonstration of effect is clear and the lowest effective concentration of oxygen is used. There is evidence that this is often less than 40 per cent, a concentration that further experience may show to be without significant danger to the eyes.[79]

Gas mixtures with high oxygen concentrations are generally used with almost all the technics of resuscitation. It is sometimes suggested that a relatively nonabsorbable gas, such as nitrogen, which might have less tendency to produce secondary atelectasis, should be used in relatively small concentrations with oxygen. Although in practice small concentrations of nitrogen would probably almost always be present, this concept needs further elucidation.

Gastric administration. In an attempt to oxygenate the blood of infants with apnea or with inefficiently functioning lungs, nonpulmonary routes of administration, particularly gastrointestinal, have been suggested and attempted. Ylppö[80] and Akerren and Fürstenberg[81] have reported successful results with gastric administration of oxygen to apneic and asphyxiated premature and full-term newborn infants. The catheters are inserted into the stomach, and oxygen, at the rate of 1 to 4 liters a minute, is administered through one, the other serving as an escape valve. In a short period, the stomach and small intestine are filled with gas, the abdomen is distended, and gas may be passed by rectum. Although the resulting distention presumably interferes with diaphragmatic movement, no serious complications, such as gastric perforation, have been reported. Akerren and Fürstenberg calculate, on theoretical grounds, that approximately 3 ml. of oxygen per minute may be absorbed from the gastrointestinal tract (compared to an estimated need of 12 to 20 ml. per minute for the average newborn infant).

In spite of additional favorable reports[82-85] on the use of gastrointestinal administration of oxygen, no critical data are available to substantiate its effectiveness. Recently, on the basis of work on dogs and puppies, Apgar and Holaday[86] suggested that much, if not all, of the effect of oxygen so administered is by a spill-over into the nasopharynx and respiratory passages. In the animal, at least, it is known that approximately 25 per cent of the cardiac output goes to the entire portal system.[87] Although the circulatory dynamics of the newborn infant may provide a peculiarly large amount of blood flow to the gastrointestinal tract, it seems unlikely that a significant amount of oxygen can be absorbed by this route. However, it should be pointed out that the advocates of this method of resuscitation have not claimed that it is effective for maintaining oxygenation, but merely advise it as a simple, safe and rapid technic that "may" oxygenate the blood sufficiently to enable the respiratory center to recover and initiate respiration.

Parenteral, nonrespiratory routes. It has been shown that an insignificant amount of absorption follows intraperitoneal and subcutaneous injections of oxygen.[88] Oxygen at the rate of approximately 0.25 ml. per kilogram of body weight per minute has been administered intravenously without harm to adults,[88] but Reissmann and Diamond[89] point out that this is not a practical route because of mechanical difficulties of producing small enough bubbles (less than 0.6 mm. in diameter). No reports on its use in newborn infants are available.

Injections of oxygenated whole blood into the umbilical vein of the human previable fetus have resulted in changes in heart activity, blood pressure and respiratory movements suggesting that such a technic might have some effectiveness in resuscitation of newborn infants.[90] Its use in this situation is being evaluated.[91]

Carbon Dioxide

The data presented in the first section of this review show that carbon dioxide is a respiratory stimulant in normal infants. A similar effect in adults has been recognized for many years and has led to the use of carbon dioxide in the resuscitation of newborn infants. However, Eastman's[19] demonstration of an elevated carbon dioxide tension in infants with severe asphyxia indicates that the use of carbon dioxide in apnea should be abandoned since it will probably be ineffective and may well contribute to further respiratory-center depression. Similarly, infants with progressive respiratory distress often have mild to moderate elevations in blood carbon dioxide tension (Table 2). Administration of carbon dioxide, therefore, seems equally contraindicated in this group of infants. Only if further studies indicate that significant apnea or later inadequate ventilation can occur in association with low or

normal arterial tensions, should 0.5 to 2 per cent carbon dioxide be tried.

Helium

Barach[92] first suggested the therapeutic use of helium with oxygen or air. Inspired helium-gas mixtures will decrease resistance due to turbulent flow because the density of the gas mixture is lower than that of oxygen or air alone.[30] Although the work of overcoming turbulence is not significant in the respiration of the normal adult and probably not in that of the normal infant, the greatly increased flow rates of infants with respiratory distress may produce significant degrees of turbulence that could be decreased by helium mixtures. Certainly, the proposal to use mixtures of helium and oxygen in the treatment of these infants deserves more careful evaluation than the clinical impressions thus far available.[93,94]

Electrophrenic Respiration

Diaphragmatic contraction by electric stimulation of the phrenic nerve was first described by Hufeland[95] in 1783. Simple electrodes applied to the intact skin of the neck have been devised, and both children and adults can be adequately ventilated by this means.[96-98] Spontaneous respiratory movements, when present, are usually inhibited, and blood pressure and cardiac output remain normal.[99,100] The duration of stimulation (inspiration) and relaxation (expiration) and the rate may be regulated by the operator.

With an electrophrenic respirator it is possible to aerate the lungs of infants who die before any spontaneous respiration takes place.[101] In apneic infants thus treated who survive, better aeration is sometimes noted on the stimulated side, an apparent indication of the effectiveness of the diaphragmatic contraction artificially produced.[102] Although the current provided by existing instruments is probably not sufficient to stimulate diaphragmatic contraction in all asphyxiated infants (particularly those most severely depressed, with associated anoxia of the respiratory muscles), more current could be provided and might extend the usefulness of the respirator.[103]

The experience of Cross and Roberts[101] in their evaluation of the electrophrenic respirator provides an excellent example of the difficulties of testing any method for resuscitation of apneic infants. They remained on call for cases of fetal distress and neonatal asphyxia in the delivery rooms of three London hospitals during a period of more than a year. They were called for 32 deliveries, but by the time they arrived, 30 of the infants had either died or recovered. Cross then lived for nine weeks in the Rotunda and Coombe hospitals in Dublin, and was thus able to treat with the respirator 27 "asphyxiated" infants among 1083 viable infants who were delivered during that interval. Of the 29 infants so treated in London and Dublin, 25 survived. In spite of the apparently encouraging results obtained by this energetic effort, Cross and Roberts were unable to judge whether neonatal morbidity or mortality might be significantly altered by the use of the respirator.

With a somewhat different apparatus Day and Sanford[102] utilized the electrophrenic respirator in 21 apneic newborn infants. Of the 11 who died, many had intracranial hemorrhage or other serious extrapulmonary conditions. The respirator was also used in 12 infants with "atelectasis" who breathed but had difficulty in maintaining adequate aeration, and 4 survived. The authors concluded that the effects were more encouraging when the device was used to stimulate the apneic infant than when it was used to support respiration.

These few reports do not allow any final evaluation, but the experience indicates that, with relatively little practice, the stimulating electrode can be properly placed, and that although more current may be needed for stimulus in apneic newborn infants than in older subjects, this may be safely used.

In the first section of this review, distinctions were made between various types of clinical problems in neonatal respiration and the procedures that might be applicable to these different problems. The principle of electrophrenic respiration should be ideally useful for apneic infants. Indeed, if the artificial stimulus is properly applied and the infant does not make respiratory movements or makes them but fails to continue after the stimulus is removed, it seems clear that irreversible central disturbances are present. If, on the other hand, there is an adequate diaphragmatic response, this appears to be a more physiologic method of inflating lungs than positive-pressure technics. Finally, if breathing has begun but progressive distress occurs, there is no reason to suppose that the infant's own musculature will perform any better under artificial drive from one phrenic nerve than under normal control.

(To be concluded)

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MEDICAL INTELLIGENCE

GLOSSOPHARYNGEAL BREATHING AS AN AID TO THE COUGHING MECHANISM IN THE PATIENT WITH CHRONIC POLIOMYELITIS IN A RESPIRATOR*

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GLOSSOPHARYNGEAL breathing, first described by Dail[1] in 1951, is a technic for ventilating the lungs that does not require the use of the muscles of respiration. Instead, the muscles of the mouth and pharynx are utilized to force air into the lungs under positive pressure. A volume of air averaging 60 ml. is trapped in the pharynx when the mouth and nasopharynx are closed. The air is then forced into the trachea by the constricting action of the pharyngeal muscles and upward displacement of the tongue. The trapped air is held in the trachea and lungs by closing of the larynx until the next volume of air is ready to be forced into the trachea. It may take twenty such maneuvers to force 1000 ml. of air into the lungs. The larynx is then opened and exhalation is carried out passively by elastic recoil of the lungs. This technic has been found to be helpful in patients with chronic poliomyelitis with impaired respiratory function.

Dail and his associates[2] have emphasized the value of glossopharyngeal breathing for increasing unassisted breathing tolerance and have mentioned its value in providing a more effective cough. It is now generally recognized that reduced pulmonary compliance‖ presents an additional problem to patients with chronic poliomyelitis whose respiratory function is impaired.[3] Recent work indicates that this reduction in compliance may be minimized or in part prevented by regular deep breathing exercises utilizing glossopharyngeal breathing.[4] Our primary concern here is with the influence of glossopharyngeal breathing on the production of an effective cough.

The normal act of coughing consists of a short inspiration followed by an immediate closure of the glottis and a forcible expiratory effort.[5] The glottis then opens, and air is pushed out at a high velocity. It is the purpose of this paper to demonstrate the effect of glossopharyngeal breathing on the peak expiratory flow in patients with impaired respiratory function and subnormal coughing mechanisms. It should not be inferred that the glossopharyngeal breather is able to obtain a normal cough.

METHODS

Nine patients from the Poliomyelitis Respirator Center with varying degrees of impaired respiratory function were studied. In the supine position, the patients coughed into a standardized pneumotachograph[6] after an unassisted maximal inspiration and also after a glossopharyngeal breath. The peak expiratory flow was recorded by a Sanborn Strain Gage Amplifier and an oscillograph.

Vital capacities were measured with a continuously recording spirometer. The pressure-ventilation relations (expressions of pulmonary compliance) were obtained from a previous study in which these patients** were subjects.[3]

RESULTS

In each patient studied, it was found that a higher peak expiratory flow was obtained in a cough after a glossopharyngeal breath than in one after an unassisted maximal inspiration. The increase was greater in patients with the greater maximal glossopharyngeal breath. In patients with better pulmonary compliance, the relative increase was greater. Thus, the increase in peak expiratory flow with a glossopharyngeal-breath cough seems to be directly related to the volume of the glossopharyngeal breath and to pulmonary compliance. In neither is the relation linear. Data obtained in our study are presented in Table 1.

Relations between peak expiratory flow with an unassisted maximal inspiration cough, with a glossopharyngeal-breath cough and with the expected rate after a normal cough are shown in Figure 1. Volume relations of vital capacity, maximum glossopharyngeal breath and expected vital capacity are shown on the

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‖Pulmonary compliance is an index of the elasticity of the lungs and thorax. It is usually expressed as the pulmonary volume change per unit of transmural static pressure applied between the alveoli and the outside of the chest wall. In this paper, it is expressed as the percentage of the predicted normal total lung capacity involved in tidal ventilation at a pressure of −25 cm. of water in a tank respirator running at 18 cycles per minute. This technic does not actually measure pulmonary compliance, since a number of variables are introduced, including airflow resistance. However, when one is dealing with a convalescent patient without airway obstruction, the technic does reflect changes in compliance and has, in addition, a very important advantage in that it can be easily and quickly carried out on the average hospital ward without special equipment other than the readily available spirometer.

**Patients J.G., A.K. and H.S. were not included in the previous study, and no compliance is recorded for them.

same percentage scale as the flow rates in Figure 1.

Discussion

Glossopharyngeal breathing appears to enhance the coughing mechanism of patients with chronic poliomyelitis with impaired respiratory function by increasing the peak expiratory flow of air. It does this in two ways: by increasing the volume of air trapped within the lung so that there is a higher intrarespiratory-tract pressure to force air out when the glottis opens; and by increasing pulmonary compliance, which we have shown to be directly related to expiratory flow.[4] The first of these is clearly seen from the measured glossopharyngeal breath and the concomitant increased peak expiratory flow after glossopharyngeal breathing in each of the patients studied. The second is demonstrated by the relatively greater increase in expiratory flow in patients with the better

Table 1. *Individual Data on Volume Relations and Peak-Expiratory-Flow Relations between Unassisted and Glossopharyngeal Breathing.*

Patient	Sex	Age	Height	Peak Expiratory Flow		Vital Capacity	Maximal Glossopharyngeal Breath	Expected Vital Capacity	Vital Capacity as Percentage of Expected Normal	Maximal Glossopharyngeal Breath as Percentage of Expected Normal Vital Capacity	Peak Expiratory Flow as Percentage of Expected Normal*		Pulmonary Compliance
				Unassisted Cough	Glossopharyngeal-Breath Cough						Unassisted Cough	Glossopharyngeal-Breath Cough	
		yr.	*cm.*	*liters/min.*	*liters/min.*	*ml.*	*ml.*	*ml.*					
W.B.	F	20	167	80	216	336	2100	3360	10	62	17	47	21.9
N.S.	M	21	188	102	324	424	3400	4700	9	64	22	69	27.3
J.G.	F	19	160	140	203	600	2500	3200	19	78	30	44	—
R.N.	M	14	162	36	100	360	1500	3100	23	48	8	22	10.3
B.W.	M	33	186	113	128	545	1100	4750	12	23	24	27	13.1
D.K.	M	29	168	99	170	400	2000	4200	10	49	21	38	17.0
A.K.	M	30	183	213	246	2030	2300	4575	44	50	46	53	—
L.C.	M	27	185	247	407	1500	3400	4625	32	73	53	88	29.2
H.S.	M	17	178	170	243	1545	2100	4450	35	47	37	52	—

*Normal peak expiratory flow taken from Barach and Smith.[5]

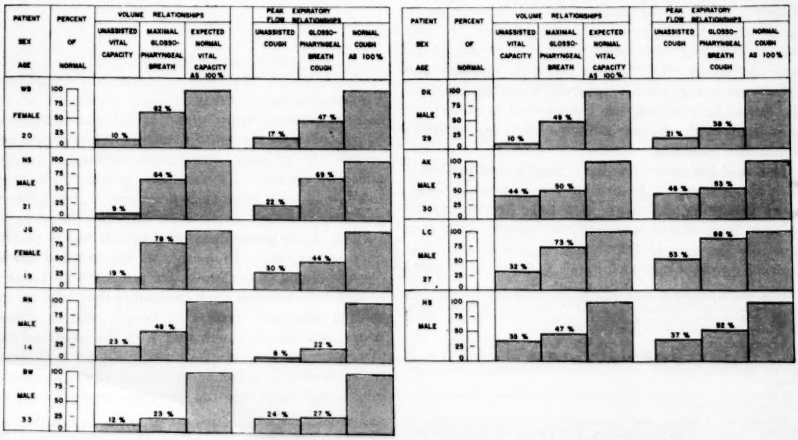
PATIENT
SEX
AGE
PERCENT OF NORMAL
VOLUME RELATIONSHIPS
UNASSISTED VITAL CAPACITY
MAXIMAL GLOSSOPHARYNGEAL BREATH
EXPECTED NORMAL VITAL CAPACITY AS 100%
PEAK EXPIRATORY FLOW RELATIONSHIPS
UNASSISTED COUGH
GLOSSOPHARYNGEAL BREATH COUGH
NORMAL COUGH AS 100%
WB FEMALE 20
NS MALE 21
JG FEMALE 19
RN MALE 14
BW MALE 33
DK MALE 29
AK MALE 30
LC MALE 27
HS MALE
10 % 62 % 17 % 47 %
9 % 64 % 22 % 69 %
19 % 78 % 30 % 44 %
23 % 48 % 8 % 22 %
12 % 23 % 24 % 27 %
10 % 49 % 21 % 38 %
44 % 50 % 46 % 53 %
32 % 73 % 53 % 88 %
35 % 47 % 37 % 52 %

Figure 1. *Graphic Illustration of the Marked Increase in Maximal Breath and Peak Expiratory Flow Achieved with Glossopharyngeal Breathing.*

pulmonary compliance (that is, N.S. and W.B., with good compliance, as compared to B.W. and R.N., with poor compliance). In patients W.B. and N.S., with vital capacities of only 333 ml. and 424 ml. respectively, the assistance given to the coughing mechanism was the most marked. It is in this group with very low vital capacities that the need for assistance is greatest. W.B., with an unassisted peak expiratory flow of 80 liters per minute, was able to increase the rate to 216 liters per minute. N.S. was able to increase it from 102 to 324 liters per minute.

Although the most dramatic aid is afforded the patients with lower vital capacities, it can be seen from inspection of the data of L.C. (vital capacity of 1500 ml.), A.C. (vital capacity of 2030 ml.) and H.S. (vital capacity of 1500 ml.) that glossopharyngeal breathing significantly increases the peak expiratory flow also, and thus can be of aid to the coughing mechanism of patients with relatively high vital capacities.

Glossopharyngeal breathing does not give the patient a normal cough. Without the subjective sensation of the "tussive squeeze," he may not consider his cough improved, but on the basis of these studies, it seems logical that ability to expel bronchial secretions would be improved. Glossopharyngeal breathing does not permit a paroxysmal cough.

Conclusions

Glossopharyngeal breathing improves the impaired cough in patients with chronic poliomyelitis with impaired respiratory function by increasing the peak rate of expiratory flow. The rise in peak expiratory flow is accomplished by an increase in the volume of air inspired before the cough and through improvement of pulmonary compliance.

Patients with very low vital capacities are helped most. Patients with relatively high vital capacities are significantly helped.

Glossopharyngeal breathing does not permit the patient to obtain a normal cough.

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BY THE LONDON POST

The Cost of Health — Vaccination against Poliomyelitis — The Battle of Diet

John Lister, M.D.

London, England

THE committee set up by the Minister of Health in 1953 under the chairmanship of the Cambridge economist, Mr. C. W. Guillebaud, to inquire into the present and prospective cost and general structure of the National Health Service has just published its report. The report has been generally welcomed by the British Medical Association because it has paid a tribute to the part played by the doctors of the country in making the service a success and has found that in general the service is being efficiently run.

For its analysis of the present and prospective cost of the health service the committee drew largely upon a detailed study prepared for it by the National Institute of Economic and Social Research. It found that the funds voted annually by Parliament are not a reliable guide to the true use of resources by the service. Though the money cost has grown every year when allowance has been made for the falling value of money, the trend of the real cost of the service has been very different, the real cost representing a steadily diminishing proportion of the national income.

The committee maintains that there is no objective and attainable standard of adequacy in the health field and that the Government must decide each year what amount of national resources may be allocated to the National Health Service, with due regard for the competing claims of the the other social services and national commitments. Once the resources have been allocated the aim must be to provide the best possible service within the limits of the allocation. The committee believes, however, that allowance must be made for a much greater capital expenditure in the future to replace outdated hospital buildings and bring others up to modern requirements.

At present it has found no evidence of widespread extravagance in the service in terms of either money or manpower. On the other hand, it believes that there are certain defects in the present organization and administration. One of the most obvious of these is the division into three major services, — the general-practitioner service, the hospital service and the local-health service, — each being separately financed. The Guillebaud committee does not think that unification is feasible under present circumstances. Others believe that the provision of adequate medical care for the "whole man" is difficult while the hospital, the general practitioner and the home nurse are each on a different payroll. Two thirds of the total money of the National Health Service is at present going to

the hospitals, emphasizing too much the care of the sick in hospital with too little emphasis on preventive medicine and home treatment. It has been suggested that many more persons could be treated at home by their general practitioners. This not only would be in line with modern medical opinion but also would help to raise the status of the general practitioner and lead to a considerable national saving, by preventing the center of gravity of medical care from shifting irretrievably from the home and the physician's office into the costly hospital bed.

* * *

A British improved variant of the Salk vaccine will be used to vaccinate between 250,000 and 500,000 children in Britain in May and June this year.

The vaccines have been prepared by two British manufacturers, — Glaxo and Messrs. Burroughs Wellcome, — who have been working in co-operation with the Medical Research Council. The vaccines differ from the American preparations in the strain of poliomyelitis virus included. The Type 1 Mahoney strain used in the preparation of the Salk vaccine is considered unsuitable and has been replaced by a modified Brunhilde strain. Both the British vaccines will contain antibiotics, the final product containing about 50 - 100 units of penicillin and 200 mg. of streptomycin per milliliter.

Vaccination will be entirely voluntary and arranged by the local-health authority. The program for 1956 will be in the nature of a trial since there will only be enough vaccine available to vaccinate about a tenth of the children in the selected age group — namely, those born during 1947-1954. The children to be vaccinated will be chosen in accordance with a centrally arranged plan designed to maintain an even spread throughout the eligible age group, which will be based on the month of birth.

Public reaction to the announcement has on the whole been enthusiastic although it is not surprising that there is a certain anxiety about the safety of the preparation. The reaction of the medical profession has been rather one of bewilderment because physicians first learnt of the vaccine through the lay press or the radio and the official circular sent to the Local Health Authorities contained no scientific information. This error of omission on the part of the Ministry of Health called forth an outspoken leading article in the *British Medical Journal* in which the Ministry was severely criticized for failing to maintain a better liaison with the profession. In replying to this criticism the Ministry maintained that the announcement was made at the earliest possible moment to allow local-health authorities to make the necessary arrangements, and stated that the *British Medical Journal* could have attended the Minister's preconference if it had wished to do so. Nevertheless, it is clear that a closer liaison between the Ministry and the profession than was evident on this occasion is essential in all matters concerning the public health.

* * *

It is perhaps in the field of dietary advice that the physician has as much power over his patient as in any other. Low-sodium, low-fat, low-calorie and low-residue diets all sound a familiar note: small, regular meals, no starch and no alcohol — again, the note of authority and warning is clear. Yet there seems to be faint signs that the dictatorial voice of dietary advice is about to be challenged.

A recent article in the *British Medical Journal* showed that patients with peptic ulcer who followed an ordinary diet recovered as quickly as those who followed a rigid regimen. Further encouragement for the "diet breaker" has come from the *Family Doctor* — the lay publication of the British Medical Association. It is pointed out that when man's ancestors stopped eating raw roots and took to cooking they lost nothing but their indigestion. It is further pointed out that a diet of nothing but fruit and salad would quickly kill us off, unless reinforced by steak and kidney pudding, fish and fried potatoes, ham and eggs, Irish stew and Lancashire hot pot.

Turning to the vexed question of tonics and vitamins, the *Family Doctor* has suggested that the addition of hypophosphites and vitamins to the diet is not necessary and that an ordinary mixed diet probably contains all the vitamins required.

Perhaps the answer is that enjoyment is nine tenths of the battle of diet. A tablet can make one man feel better as a whisky and soda can persuade another that the evening is growing brighter. Furthermore, there are times when instinct is better than medical advice, and it would be well for physicians to remember, when giving dietary advice, that no patient is likely to follow it unless he believes that it is really necessary and secondly that it is not too unpalatable. Moderation in all things is perhaps good advice both for the doctor advising the diet and for the patient following it.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42131

PRESENTATION OF CASE

A fifty-three-year-old German was admitted to the hospital because of weakness and fatigue.

Three months before admission the patient had a severe upper respiratory infection requiring bed rest for one week. Jaundice and dark urine were noted. The jaundice cleared after several days, but the urine remained dark. Two months before entry he had another upper respiratory infection, after which he felt very weak. One month later, because of continuing weakness, fatigue, shortness of breath and icteric scleras, he was admitted to another hospital for two weeks. Since then anorexia and an 8-pound weight loss had been noted.

Twenty years previously when the patient had worked in a zinc mine he was exposed to a heavy concentration of TNT fumes as well as to dust containing zinc and nickel. About fifteen years before entry he had worked in a leather-dying plant. There had been no exposure to benzene. A diffuse skin eruption over the arms and torso had been present for about ten years.

Physical examination showed a well nourished man with moderate scleral icterus. There was a diffuse macular skin rash over the trunk and arms. The teeth were carious, and the tongue was normal. The liver edge was felt 5 fingerbreadths below the right costal margin; the upper border of liver dullness was at the seventh intercostal space. The spleen was palpable 2 fingerbreadths below the left costal margin. There was no lymphadenopathy. Rectal examination was negative.

The temperature was 100°F., the pulse 100, and the respirations 18. The blood pressure was 140 systolic, 70 diastolic.

The urine showed a trace of bile with the Harrison spot test. The urinary urobilinogen was 11.8 Ehrlich units. Examination of the blood revealed a hemoglobin of 9.4 gm. per 100 ml., a hematocrit of 32 per cent and a red-cell count of 3,090,000. The serum iron was 330 microgm., and the total iron-binding capacity 380 microgm. per 100 ml., and saturation 87 per cent. The nucleated-cell count was 6500, with 7 per cent erythroblasts, 38 per cent normoblasts, 5 per cent myeloblasts, 8 per cent band forms, 20 per cent neutrophils, 2 per cent eosinophils and 20 per cent lymphocytes. The erythrocytes were slightly macrocytic and slightly hypochromic and showed moderate basophilia, with marked aniso- and poikilocytosis. The platelets were normal in number, with some giant forms present. The reticulocyte count was 7.2 per cent. Examination of the bone marrow revealed 5 per cent myeloblasts and promyelocytes, 13 per cent myelocytes, 13 per cent metamyelocytes and bands, 0 per cent neutrophils, 2 per cent lymphocytes and 67 per cent erythroblasts and normoblasts. Megakaryocytes were normal. The erythrocyte osmotic fragility was normal. Direct and indirect Coombs tests were negative. The cold-agglutinin titer was 1:8. The serum bilirubin was 1.1 mg. direct and 3.4 mg. total, and the uric acid was 11 mg. per 100 ml. Cephalin flocculation was ++ in forty-eight hours. The nonprotein nitrogen, acid phosphatase, total protein, albumin, globulin and prothrombin content were normal. An "LE" test was negative. Three stools were guaiac negative. Except for a slightly enlarged spleen and a small hiatus hernia, the x-ray films, including an upper gastrointestinal series, intravenous pyelogram, barium-enema examination, Graham test and chest and skull examinations, were normal.

Biopsy of an inguinal lymph node showed fibrosis. Cortisone, 300 mg. daily, was given orally. The nucleated-cell, reticulocyte, platelet and differential counts, hemoglobin and urinary urobilinogen remained about the same. The serum bilirubin was 1.5 mg. per 100 ml. total on the twentieth hospital day. The temperature ranged between normal and 100°F.

Whole-blood transfusions were given, and an operation was performed on the twenty-sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. FRANK H. GARDNER*: I suppose that this man was still a leather worker; is that correct?

DR. LEONARD ATKINS: He was a truck driver.

DR. GARDNER: The patient entered the hospital with a three-month history of jaundice. From the symptoms I believe that I can assume that he had anemia during that period. The onset with a respiratory infection suggests that he had a hemolytic episode associated with an atypical pneumonia, but I am unable to confirm such a diagnosis from the data available. Is there any further information about the previous hospital admission elsewhere?

DR. ATKINS: There was not much information about the hematologic work up.

*Senior associate in medicine, Peter Bent Brigham Hospital.

DR. GARDNER: One can doubt if this was a hemolytic reaction associated with atypical pneumonia since the patient did not have a high titer of cold agglutinins, although in a three-month period, these usually revert to normal. A hemolytic reaction is usually fairly acute and self limited and should have terminated by the time that he was seen in this hospital. I cannot exclude it, for we see a number of patients who have a history that suggests atypical pneumonia and have a chronic hemolytic anemia but they almost always have a high titer of cold agglutinins to confirm our suspicions. I do not think the past history of industrial exposure to zinc and nickel contributed to the hematologic problem. Possibly, the exposure to nickel initiated the chronic skin rash. I probably cannot place much emphasis upon the influence of the exposure to benzene since he had not worked in the leather industry for many years. Although he probably had not been exposed to benzene, one wonders whether he was a clerk or actually worked in the dyeing vats.

DR. ATKINS: We do not know that.

DR. GARDNER: Some of the earlier studies done in this hospital[1] seemed to indicate that immediate exposure with benzene was not always important.

The laboratory data probably allow me to do as much with the diagnosis as I can. There was evidence of a moderate increase in blood destruction characterized by an increased indirect serum bilirubin and urinary urobilinogen. A moderate reticulocytosis was associated with a marked proliferation of normoblasts and early granulocytes in the peripheral blood, marked normoblastic activity in the bone marrow and an increased percentage of myeloblasts in both the peripheral blood and the bone marrow. These changes were associated with hepatosplenomegaly. I gather, Dr. Hanelin, that the x-ray films are helpful to the extent outlined in the protocol.

DR. JOSEPH HANELIN: The spleen seems to be slightly enlarged, and there is confirmation of the palpably enlarged liver.

DR. GARDNER: With the enlarged liver there was no evidence of severe liver disease.

This patient did have a leukoerythroblastic response in the peripheral blood, which is somewhat unusual in adults with an idiopathic hemolytic anemia. In fact I think that one can immediately question the mechanism of a hemolytic anemia whenever there is a marked increase in erythroblastic forms in the peripheral blood. As a rule of thumb with a hemolytic anemia, more than 7 per cent reticulocytes should be present in the peripheral blood. If less are present one should immediately be suspicious that the hemolytic anemia is secondary to some other process. The erythroblastic proliferation in the bone marrow also was somewhat out of line with the reticulocyte response seen in the peripheral blood. Therefore, I must assume that this patient had a bizarre bone-marrow disorder rather than a simple stress response to hemolysis. I think that whenever there is a low-grade reticulocytosis and normoblastic proliferation in the peripheral blood, one should immediately consider erythremic myelosis or di Gugliemo's disease, which we are always seeking but seldom find. This man did not have the early immature erythroid forms in the peripheral blood or bone marrow that I consider necessary to confirm the presence of that disorder. Finally, I believe that the normal maturation of the erythroblasts in the bone marrow allows me to exclude erythremic myelosis.[2]

Can we attribute the peripheral-blood response to any other irritants that might stimulate a leukemoid reaction? There was no evidence on the radiologic examination of any chronic infection or tumor. Certainly, intensive efforts were made to find them. The biopsy of the lymph node did not reveal lymphoma although I am not sure that the lymph node removed was enlarged since it was not described in the physical examination. There was certainly no suggestion of a retroperitoneal tumor in the intravenous pyelogram. Moreover, the bone-marrow aspiration revealed no tumor cells. The bone marrow did contain an increased percentage of myeloblasts. Dr. Atkins has kindly allowed me to see the slide of bone marrow; I agree that erythroblasts were present, and I wonder if this reflected an early invasion of the bone marrow in a leukemoid response to a myelogenous leukemia. I believe the leukoerythroblastic response in the peripheral blood was stimulated by the leukemic invasion of the bone marrow. Likewise, the patient had a high level of uric acid in the serum.

I believe I can exclude the leukemoid reactions associated with infection, for there was no evidence of the most common infection with which the myelogenous response occurs, — namely pulmonary or disseminated tuberculosis, — nor was there evidence of tumor of the gastrointestinal tract, which frequently may cause the same peripheral-blood picture. Likewise, it would be rare for a leukemoid response to infection, especially tuberculosis, to produce only myeloblasts in the peripheral blood. Usually, myelocytic leukemoid responses to infection or tumor result in myelocytes and metamyelocytes with only a rare blast form. The fact that the patient was relatively afebrile is good evidence that he did not have tuberculosis of the spleen, which may be associated with a leukemoid response.

The congenital type of hemolytic jaundice at this age can be excluded because of the absence of a past history of hemolytic episodes. Certainly, it would be rare for a patient with congenital hemolytic jaundice to reach this age without previous episodes of jaundice or gallstones. He did not have spherocytes in the peripheral-blood smear, and he had normal osmotic fragility. Although he probably had a secondary type of acquired hemolytic anemia as an irritative response, it was not associated with a so-called immune mechanism, for the Coombs test was negative, and the cold

agglutinins were normal. Many patients with hemolytic anemia secondary to tumor do not have measurable agglutinins. The high serum iron and increased saturation of the iron-binding protein leads one to wonder about hemochromatosis. These findings were associated with the rapid turnover of the iron stores, which is not uncommon in disease in which blood destruction with improper utilization of the iron by the bone marrow occurs. Hemochromatosis has been observed with acquired hemolytic anemia, but the clinical picture and the absence of other stigmas of the disease exclude this diagnosis.

The patient was treated with cortisone, and twenty days later the serum bilirubin had decreased quite markedly from a total of 4.5 to a total of 1.5 mg. per 100 ml. I assume that that indicated a decrease in blood destruction. Possibly, he was not observed long enough for improvement in the blood values to be noted. If he had an irritating tumor of the marrow, the blood destruction may have been decreased without a rapid increase of blood production during the period of observation.

I assume that the operation performed was a splenectomy. I believe that this patient had a secondary type of acquired hemolytic anemia. I would be anxious to study the bone marrow further by examination, either aspiration or trephine biopsy, to determine whether the changes could be more clearly defined while he was receiving steroids. I suspect that a splenectomy for a secondary type of acquired hemolytic anemia might be helpful; I do not believe that the disease was of the idiopathic, acquired type for which splenectomy seems to be more favorable. I believe that the underlying cause probably was myelogenous leukemia.

DR. ROBERT E. SCULLY: Would anyone like to comment or offer another diagnosis?

DR. BERNARD M. JACOBSON: Dr. Gardner, there are three laboratory examinations on which you did not comment; I wish you would help us explain those. There was an extremely high urinary urobilinogen of 11 Ehrlich units; in a two-hour specimen taken from 1 to 3 p.m., the upper limit of normal is about 1.3 Ehrlich units. Would you not be questioned very seriously by Dr. Cecil Watson, of Minneapolis, whether this represented a hemolytic process or whether it indicated liver dysfunction? The other two points on which you did not comment are the marked anisopoikilocytosis of the red cells and the markedly elevated serum uric acid — the normal value in this laboratory for a man is up to 6 mg. per 100 ml.

DR. GARDNER: My comments on the high urinary urobilinogen are not going to be complete. I believe that distortion of erythroid maturation is often the effect of bone-marrow irritation — that it reflects rapid hemolysis or destruction of hemoglobin pigment that does not necessarily have to be the destruction of a mature red cell. The high Ehrlich units are indicative of the pigment turnover. The anisopoikilocytosis of the peripheral smear is a reflection of the leukemoid response. I mention this observation because in my thinking about the peripheral blood it was very important. The variation in size of the red cells is often seen when there is bone-marrow irritation. The variation in shape is more frequently seen with extramedullary hematopoiesis. Both can be present if there is diffuse bone-marrow invasion by tumor. The high uric acid, I think, was the result of the myelogenous leukemia.

DR. SCULLY: What was your preoperative impression, Dr. Jacobson?

DR. JACOBSON: All of us thought as Dr. Gardner did that the hemolytic components, although certainly present, could not explain the entire clinical and blood picture. The number of nucleated red cells in the peripheral blood was so enormous in comparison with the only mild elevation of the reticulocytes that we all believed that the normoblasts in the peripheral blood represented bone-marrow irritation or extramedullary disturbance. We did all we could to rule out metastatic cancer to the bone marrow. Initially, the bone-marrow picture did not appear to us to show enough immature myeloid cells to suggest myelogenous leukemia although we do accept that concept. The vast number of nucleated red cells in the peripheral blood with the marked normoblastic proliferation in the bone marrow brought up the question of another variant of leukemia involving the red-cell elements as well as the granulocytes — the so-called erythroleukemia. I personally was enough impressed with the anisopoikilocytosis and the hypochromia of the red cells to venture a diagnosis of reasonably benign chronic idiopathic (agnogenic) myeloid metaplasia. However, we realized at that time that the splenomegaly was not as great as one would expect in the ordinary case. We thought that a serum uric acid of 11 mg. per 100 ml. favored that diagnosis rather than myelogenous leukemia. In our experience the serum urate level in chronic myelogenous leukemia is less commonly elevated, and when it is, it is around 7 or 8 mg., whereas in the vast majority of cases of myeloid metaplasia of the idiopathic variety, the uric acid is markedly elevated and there is a very high incidence of clinical gout. Of course, splenectomy was done to try to mitigate the hemolytic component even though we were dubious about an adequate therapeutic response.

DR. SCULLY: We are going to tell you the clinical course of the patient after the splenectomy and then ask you to comment again, Dr. Gardner.

DR. ATKINS: The spleen was twice the normal size, weighing 325 gm., and there was also an accessory spleen measuring 1.5 cm. in diameter. Microscopically, the architecture of the spleen was preserved; there was a diffuse infiltrate of large numbers of normoblasts and erythroblasts throughout the splenic sinusoids and the pulp. In addition there were

also many blast forms, presumably myeloblasts as well as myelocytes and some metamyelocytes. A few hematopoietic islands were noted. Table 1 shows the peripheral-blood picture during the subsequent course. Immediately after the splenectomy there was a transient drop in the platelets, which returned to normal after a period of about two weeks. Cortisone was continued postoperatively; the dosage was gradually tapered until the eighteenth postoperative day, when

TABLE 1. *Peripheral-Blood Counts.*

TIME OF TEST	HEMOGLOBIN	RETICULOCYTES	TOTAL NUCLEATED-CELL COUNT	PERCENTAGE OF NUCLEATED ERYTHROID CELLS
	gm./100 ml.	%	*per cu. mm.*	
Before operation	9.4	7.2	6,500	45
1 wk. after splenectomy	12.0	7.0	17,000	20
3 mo. after splenectomy	10.0	28.4	43,000	95
5 mo. after splenectomy	9.0	12.0	51,000	85
11 mo. after splenectomy	9.1	5.3	110,500	95
1 yr. after splenectomy*	8.7	—	280,000	50

*Terminal.

the patient was discharged with no specific therapy. After the splenectomy the hemoglobin was 12 gm. per 100 ml., — transfusions had been given, — the reticulocytes were 12 per cent, and the total nucleated-cell count in the peripheral blood was 17,000, with 1 per cent myeloblasts, 2 per cent promyelocytes, 3 per cent metamyelocytes, 1 per cent eosinophils and 17 per cent lymphocytes; 20 per cent were nucleated red cells, mostly normoblasts and a lesser number of erythroblasts. Three months later the hemoglobin was 10 gm. per 100 ml., the reticulocyte count was 28.4 per cent, and the total nucleated-cell count had risen to 43,000. At this time 95 per cent of these cells were erythroid — mostly normoblasts and erythroblasts. About three months after discharge the patient was readmitted to the hospital because of an abscess in the right supraclavicular region and was hospitalized for about three months, during which abscesses developed in the left triceps areas and over the left thigh. *Staphylococcus aureus* was cultured from all of these, and at one time the blood culture grew out *Staph. aureus*. He was treated with antibiotic therapy; the abscesses were incised and drained; he was discharged improved. During another admission, five months after splenectomy, the total nucleated-cell count had risen to 51,000, of which 85 per cent were nucleated red cells. The final admission was for oral sepsis. At this time he had generalized lymphadenopathy, markedly decreased platelets and a bleeding tendency. Terminally, the nucleated-cell count was 280,000, of which 50 per cent were nucleated red cells, and the remainder of the cells were mostly myeloblasts.

Table 2 shows the bone-marrow picture. After the splenectomy there was a shift to the left in the myeloid series, with 21 per cent myeloblasts and promyelocytes, 26 per cent myelocytes and 12 per cent metamyelocytes and band forms. During the admission for the abscesses, five months after splenectomy, there were 46 per cent erythroblasts and normoblasts, 11 per cent myeloblasts and promyelocytes, 28 per cent myelocytes, 10 per cent metamyelocytes and band forms and 5 per cent neutrophils. Terminally, the marrow picture showed 41 per cent erythroblasts and normoblasts, 54 per cent myeloblasts and 3 per cent promyelocytes — a marked shift to the left.

DR. SCULLY: Dr. Gardner, should you like to comment further?

DR. GARDNER: It is an interesting case. I think I should go along with Dr. Jacobson's reasoning at the time. I do not believe that I have ever seen such a high percentage of myeloblasts in the bone marrow in myeloid metaplasia. The smear that Dr. Atkins let me look at contained very immature, malignant-looking tumor cells. Certainly, it takes a long time to accumulate many of these cases. I actually excluded myeloid metaplasia after looking at that bone marrow. I did not believe that we could use that as an explanation and had to say that the anisopoikilocytosis was due to a tumor irritation — a vague word, I know. I do recall a man on whom we did a splenectomy for tumor, who responded in this way but not to this degree. This response was tremendous. I do not think that I have ever seen a case with this amount of normoblastic response after splenectomy. Certainly, patients with myeloid metaplasia whose spleens we have intentionally removed to alleviate bleeding problems have had a greater normoblastic response than we could interpret or understand. I still do not understand why some patients who have myelofibrosis of the bone marrow and an absent spleen are able to proliferate normoblasts — probably from other metaplastic sources. I assume that we have merely removed the filter or the brake for these ab-

TABLE 2. *Bone Marrow.*

TIME OF TEST	ERYTHROBLASTS & NORMOBLASTS	MYELOBLASTS & PROMYELOCYTES	MYELOCYTES	METAMYELOCYTES & BAND FORMS	NEUTROPHILS	LYMPHOCYTES
	%	%	%	%	%	%
Before operation	67	5	13	13	0	2
3 days after splenectomy	28	21	26	12	13	0
5 mo. after splenectomy	46	11	28	10	5	0
1 yr. after splenectomy*	41	57	2	0	0	0

*Terminal.

normal cells so that they easily enter the peripheral blood.

DR. JACOBSON: What is your final diagnosis?

DR. GARDNER: It is still myelogenous leukemia. What is your idea of myeloid metaplasia? Would it alter your ideas if you saw megakaryocytes in the surgical specimen?

DR. JACOBSON: Yes. As you can gather, we changed our speculative diagnosis after splenectomy to a form of malignant leukemic proliferation. I think, in summing up, I might mention Dr. William Dameshek's useful concept about the myeloproliferative disorders: we can satisfy all proponents of various diagnoses, if we say that this man had a malignant proliferation, which can go by various names at different stages. The most benign is a pure polycythemia rubra vera, then myeloid metaplasia, chronic myelogenous leukemia, erythroleukemia or erythremic myelosis of di Gugliemo and other intermediary syndromes. It is sometimes difficult to determine when a case of pure polycythemia with leukocytosis changes to myelogenous leukemia. Possibly, in the future, use of the alkaline phosphatase stains may help. I think that we can satisfy everybody by concluding that this man had a malignant process of the erythroid and myeloid systems. During the last few days of life, the blood smear was that of an acute myeloblastic leukemia, but the 50 per cent myeloblasts in the peripheral blood was only a terminal thing.

DR. GARDNER: Do you think that there is such a thing as erythremic myelosis?

DR. JACOBSON: If by that you mean a malignant tumor of the erythroid series, yes.

CLINICAL DIAGNOSES

Myeloid metaplasia (presplenectomy).
Myelogenous leukemia, with marked erythroid hyperplasia, ?erythroleukemia (postsplenectomy).

DR. FRANK H. GARDNER'S DIAGNOSIS

Myelogenous leukemia.

ANATOMICAL DIAGNOSES

Myelogenous leukemia.
Hemorrhages into gastrointestinal tract, kidneys and brain.

PATHOLOGICAL DISCUSSION

DR. ATKINS: At autopsy there was evidence of recent bleeding in the oral cavity, gastrointestinal tract, kidneys and brain. There were also abscesses in the mouth, in the right submandibular region and in the right shoulder. There was generalized lymphadenopathy; the lymph nodes measured 3 or 4 cm. in diameter and appeared yellowish gray, with hemorrhagic areas. The liver was more than three times the normal size, weighing 5200 gm., and was brown, with diffuse, grayish-white leukemic infiltration. The bone marrow of the ribs, vertebras and femurs was red. There were two recent yellow infarcts in the left ventricle of the heart, each of which measured 1 cm. in diameter. The gall bladder contained numerous small, friable, black stones averaging 1 mm. in diameter. There were grossly obvious leukemic infiltrates measuring up to 2 cm. in diameter throughout the kidneys. Microscopically, all the organs showed leukemic infiltration. The bone marrow was markedly hyperplastic. The hyperplasia was predominantly myeloblastic; there were large numbers of nucleated red cells as well. No megakaryocytes were seen. In the other tissues the infiltrate was predominantly myeloblastic with numerous blast forms and lesser numbers of myelocytes and metamyelocytes as well. There were comparatively few erythroblasts and normoblasts compared to the cells of the myeloid series. The architecture of the lymph nodes was partially preserved, and scattered follicles were seen, but here again there was a diffuse infiltration with the leukemic process. The blood vessels in all the organs were packed with immature cells of both the erythroid and myeloid series. Because of the markedly abnormal proliferation of both the myeloid and erythroid series we believe that this patient possibly was an example of erythroleukemia clinically, although the terminal picture at autopsy was that of myelogenous leukemia.

DR. GARDNER: The clinical and laboratory observations may be compatible with a diagnosis of erythroleukemia. I believe that these manifestations are a bizarre complication of myelogenous leukemia. Rarely do we have an opportunity to study this unusual type of bone-marrow dysfunction. The diagnosis of erythroleukemia may depend on the interval when the neoplastic process is observed. Certainly, the prolonged survival of these patients today with transfusions and antibiotic therapy may allow us to have a more complete understanding of the process in the future. I have believed that these patients terminally would have only evidence of myelogenous leukemia if they survived the initial period of erythroblastic hyperplasia.

Accelerated erythropoiesis is frequently observed in myelogenous leukemia and may approach or surpass the leukopoiesis.[3] Likewise, one may anticipate a marked erythroblastic infiltration in the liver and spleen. Moeschlin[4] has emphasized the fact that the bone marrow should have extensive infiltration of erythroblasts for the diagnosis of erythroleukemia to be considered. I am not certain that the autopsy observations would fit this classification.

DR. SALOMON HAKIM: The findings in the central nervous system in this case reflect the pathology seen in the other organs. The changes were the leukemic infiltrates and the results of the hemorrhagic tendency with bleeding into the parencyhma and into the sub-

arachnoid space. There was a hemorrhage in the right cerebellar hemisphere, which had partially ruptured through its superior surface. The cerebellum showed prominent coning of its inferior surface. In the cerebral hemispheres there were several small, scattered, hemorrhagic areas ranging in size from 2 to 6 mm. in diameter. Leukemic nodules of various sizes were present around the vessels and occasionally were associated with slight extravasation of blood.

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CASE 42132

Presentation of Case

A fifty-nine-year-old factory supervisor was admitted to the hospital because of vomiting.

Eleven months previously there were episodes of regurgitation unassociated with nausea or other symptoms over a period of three weeks. He was well over the next five months except for colds more frequently than usual. Five months before admission he suddenly noted a sensation of heat welling up into the head from the neck associated with marked perspiration of the face and extremities, unsteadiness, irregular movements of the surroundings and blurring of vision. After an hour in a sitting position he felt well. About four months before entry he noted gradually increasing pain anteriorly in the right flank that was relieved by his changing position. Otherwise, he remained asymptomatic until eight weeks before entry, when he had three episodes of violent vomiting preceded by flushing, heat, unsteadiness, irregular motions of the environment without true vertigo, blurring of vision and a pressure sensation in the epigastrium. These episodes were unassociated with headache, tinnitus, palpitations, speech disturbances, unconsciousness, muscular weakness, food intake, position, smoking, time of day or activity. In between attacks he felt well. Physical examination at this time was negative. X-ray films were said to have been negative except for a lesion of the right kidney. During the four weeks before admission there were five similar episodes. There was no weight loss, change in bowel habits, hematemesis, melena or urinary symptoms. There had always been almost total deafness in the left ear.

Physical examination showed a well nourished man with almost total deafness in the left ear. Examination of the chest was negative. There was moderate deep tenderness in the right flank anteriorly. No abdominal masses were felt. Neurologic examination was negative.

The temperature was 98.4°F., the pulse 78, and the respirations 18. The blood pressure was 142 systolic, 84 diastolic.

The urine gave a + test for albumin; the sedi-

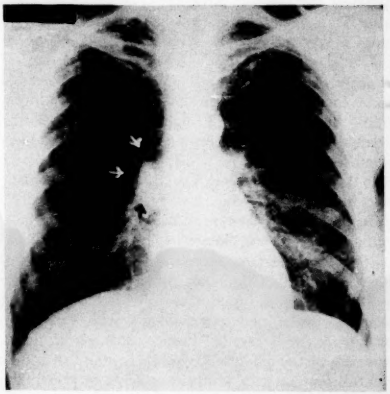

FIGURE 1. *Posteroanterior View of the Chest, Showing an Ovoid Density in the Anterior Segment of the Right Upper Lobe (Arrows).*

ment contained 5 red cells and 3 white cells per high-power field. Examination of the blood revealed a

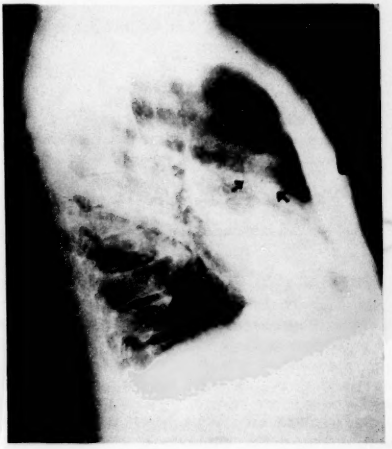

FIGURE 2. *Lateral View of the Chest, Showing the Ovoid Density Seen in Figure 1 (Arrows).*

hemoglobin of 15.8 gm. per 100 ml. and a white-cell count of 8200. The nonprotein nitrogen was 37 mg., and the fasting blood sugar 100 mg. per 100 ml. A

stool specimen was normal in color and gave a negative guaiac test. X-ray films of the chest demonstrated a soft-tissue mass measuring 4 cm. by 3 cm. by 3 cm. in the anterior segment of the right upper lobe (Fig. 1 and 2); within this mass there were areas of calcification; its upper margin was thin walled, and it appeared to contain air; it was thought that a fluid level was present, but films in different positions revealed no shift of the line; the heart was normal. An abdominal film showed a mass approximately 15 cm. in diameter lying to the right of the twelfth thoracic and upper three lumbar vertebras; there appeared to be a few flecks of calcification in the margin of the mass medially and inferiorly; the psoas shadow was obliterated in the region of the mass; the right kidney was not adequately visualized; the left kidney appeared normal; the bones were normal. Intravenous pyelograms demonstrated normal-appearing urinary passages on the left; on the right side the kidney was rotated laterally and upward, and the ureter lay adjacent to the medial margin of the mass, which involved the lower portion of the right kidney (Fig. 3).

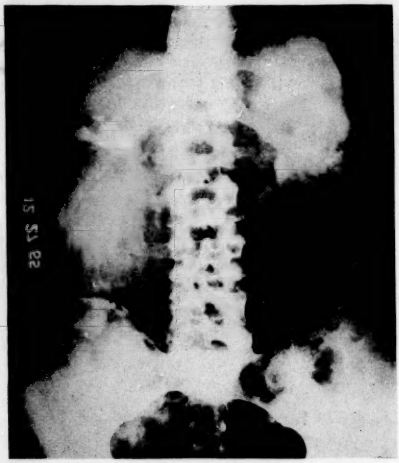

FIGURE 3. *Intravenous Pyelogram, Showing a Large Mass within the Inferior Aspect of the Right Kidney Causing Upward Displacement of the Renal Pelvis and Calyxes and Medial Displacement of the Ureter.*
Calcification is visible in the periphery of the mass, particularly inferiorly (arrows).

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARTIN B. LEVENE*: The x-ray films indicate that there are lesions in two areas, the right retroperitoneal area and the anterior segment of the right upper lobe of the lung. The clinical history suggests the probability of a lesion in a third area — namely, the brain, probably in the vicinity of the third ventricle or hypothalamus. The episodes of flushing, a sensation of heat, nausea, vomiting and blurring of vision that occurred periodically with normal intervals between attacks suggest either an irritative focus at or near the third ventricle, with periodic discharge, or possibly periodic obstruction of outflow of cerebrospinal fluid from the third ventricle. In addition, I have to consider the possibility of a functioning tumor such as a pheochromocytoma arising in the retroperitoneal chromaffin tissue, but the x-ray films help me discard the latter possibility.

I should like to turn to the films of the abdomen. The film from the upper gastrointestinal series done two or three weeks before admission demonstrates anterior displacement of the second portion of the duodenum by a mass. The follow-up films taken at some time after the upper gastrointestinal series show no obstruction to the passage of barium through the small bowel. The major portion of the barium is now strung out through the proximal colon. Again, the bowel, this time the hepatic flexure, is displaced downward by the mass. In the plain films of the abdomen the mass is not well outlined but appears as an area of increased density in the right side, obliterating the psoas-muscle shadow. It is calcified more than one would expect from the description in the protocol. There is considerable calcification — very fine flecks of calcification — in the periphery of the mass. The intravenous urographic examination nicely outlines the collecting system of the right kidney, which has been displaced upward and is somewhat compressed but shows no signs of invasion. The ureter is displaced medially. Occupying the lower pole of the right kidney is the same partially calcified mass that was visualized on the plain film (Fig. 3). From its appearance on the films I can conclude that the lesion is intrinsic to the lower pole of the right kidney.

It is possible that this lesion in the kidney was a separate entity not connected with the remainder of the clinical picture. A simple cyst of the kidney could produce this appearance, but it is unusual to see that much calcification in a simple cyst. If I consider the kidney lesion as part of the entire picture, however, the first possibility that comes to mind is a malignant tumor of the kidney, the most common of which, in a person of this age, is renal-cell carcinoma. Renal-cell carcinomas grow slowly, calcify and metastasize to lung and to brain. It could fit this picture quite well. It would be helpful to see invasion or destruction of part of the calyceal system, but I cannot exclude such a lesion because of the absence of such invasion. I doubt that the renal lesion represented any form of metastatic lesion from a primary lung tumor. I think that it was primary in the kidney and that the other manifestations of the disease were secondary.

*Clinical assistant in radiology, Massachusetts General Hospital.

What else besides a malignant tumor of the kidney might produce such a picture? Tuberculosis? I have never seen tuberculosis that presented this type of lesion in the kidneys. It is true that it occasionally produces a rounded, calcified mass, but almost invariably it involves the calyceal system or pelvis. Moreover, I think that a tuberculous mass would be unlikely to attain this size with preservation of so much normal kidney above it. It is true that tuberculous lesions can result in tuberculomas in the lung and brain.

Echinococcus disease is another possibility. This disease is caused by the tapeworm, *Taenia echinococcus granulosus;* the usual host is the dog, although other animals may be, and even man occasionally is, the intermediate host. It is uncommon in people who have lived all their lives in the United States; it is common in New Zealand, Australia, Uruguay and Argentina. It would be interesting to know if this patient had ever been outside the country and whether he was foreign born.

DR. BENJAMIN CASTLEMAN: He was born in Massachusetts and lived all his life here.

DR. LEVENE: It would also be helpful to know what the percentage of eosinophils in the differential count was.

DR. CASTLEMAN: There were 6 per cent eosinophils.

DR. LEVENE: I shall not give a detailed discussion of renal echinococcus cysts since Dr. Walter Kerr* covered that subject thoroughly not too long ago at one of these conferences. Suffice it to say that the renal lesion in the patient under discussion is compatible with and suggestive of an echinococcus cyst that had started in the kidney parenchyma, expanded and calcified around the periphery. It would be of help to be able to say that some of the smaller calcifications represented calcifications in a daughter cyst, but I am unable to do so.

At this point I shall have to turn to the films of the chest in an attempt to differentiate metastatic renal-cell carcinoma and echinococcus cyst. As described to us in the protocol, there is a mass in the anterior segment of the right upper lobe that, in the posteroanterior projection, lies over the right hilus (Fig. 1). There is a straight line across the top of the homogeneous portion of the mass that suggests a fluid level and above it an arched, thin white line. Similar lines are present in the lateral view, although they do not show as well, and are probably shown best on the spot films. The fact that the line suggesting a fluid level apparently failed to change in position when the patient was maneuvered into various positions helps me decide that this was not a cyst filled with a thin, movable fluid. A second radiolucent area below that that was not mentioned in the protocol is surrounded by thin, white zones similar to those at the top of the first lesion. I think this represents another cyst. I believe that the first lesion mentioned was a secondary echinococcus cyst that had been partially evacuated. This appearance has been described as fairly characteristic of such lesions. Apparently, the pericyst is fairly rigid and retains its arched appearance as the cyst is evacuated while the cystic membrane collapses with the remainder of the contents of the cyst. I think the other cystic lesion below the first was a cyst that had been completely evacuated. The patient was said to have frequent colds; I do not know whether there were episodes of coughing. If so, they may have been associated with the drainage of the second cyst.

In conclusion I wish to name as my choice a primary echinococcus cyst of the right kidney, with secondary lesions in the lung and probably also in the brain.

DR. ALFRED KRANES: I was intrigued by the attacks of flushing, nausea and vomiting. If these attacks were related to the tumor masses, one would have to consider seriously metastatic carcinoid, although I have never heard of carcinoids in this area, nor do I think that they calcify. These attacks are suggestive of what has been described in other patients with metastases from carcinoid.

DR. CASTLEMAN: I believe that all the patients who have had flushing with carcinoids (argentaffinomas) have had large metastases in the liver from a primary tumor of the small bowel.

DR. HOLLY SMITH: Are not such attacks as that sometimes described in echinococcus disease due to the seeding of the blood — an anaphylactic reaction?

DR. CASTLEMAN: I do not know.

DR. HERMANN K. SCHUELER: The physician who saw this patient first thought he had a Menière complex and treated him for it.

CLINICAL DIAGNOSES

Calcified cyst of right kidney.
Calcified mass in lung.

DR. MARTIN B. LEVENE'S DIAGNOSIS

Echinococcus cyst of kidney, with involvement of lung and ? brain.

ANATOMICAL DIAGNOSES

Papillary cystadenoma of kidney.
Bronchogenic cyst.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The urologist, Dr. Wyland F. Leadbetter, and the thoracic surgeon, Dr. J. Gordon Scannell, operated on the patient together. Dr. Leadbetter removed the mass in the kidney, and Dr. Scannell did a wedge resection of the lesion in the lung. The large mass in the abdomen, including the kidney,

*Case Records of Massachusetts General Hospital (Case 41462). *New Eng. J. Med.* **253**:878-881, 1956.

was removed quite easily. In the lower pole of the kidney was a tumor, 10 by 12 by 8 cm., with a thick capsule that contained about 180 ml. of hemorrhagic fluid and blackish-gray, shiny, coarsely granular material, as well as foci of calcification (Fig. 4). The

FIGURE 4.

tumor did not invade the renal tissue beyond the capsule. Microscopically, the wall of the cyst was thick and fibrotic, and the cyst contained papillary fronds covered with well differentiated epithelial cells — a perfectly benign papillary cystadenoma into which there was a good deal of hemorrhage (Fig. 5). Such papillary tumors are likely to have foci of calcification. The lesion in the lung was a cystic structure filled with mucopurulent material and lined with normal bronchial epithelium, a bronchogenic cyst. In other words, this patient had two benign lesions, one in the kidney and one in the lung, that were not related to each other.

DR. JACOB LERMAN: Or to the symptoms?

DR. CASTLEMAN: Or to the symptoms.

DR. LERMAN: Were there two cysts in the lung?

DR. CASTLEMAN: I do not know; the surgeons opened the specimen. We could not identify two cysts. There was a focus of calcification in the cyst, and I think it was a true bronchogenic cyst rather than one that had developed as the result of infection, although I cannot be absolutely sure.

A PHYSICIAN: What happened to the patient's symptoms?

DR. CASTLEMAN: The patient has been discharged asymptomatic. Dr. Schueler, can you tell us what has happened since discharge?

FIGURE 5.

DR. SCHUELER: The patient was seen by Dr. Leonard W. Cronkhite two months after the operation; he had been entirely well since the operation and had returned to work.

DR. CASTLEMAN: We do not know whether the symptoms suggestive of a lesion in the cerebellum or pons may reappear later. I do not know what is in the brain.

DR. SCHUELER: It is possible that he had Menière's disease.

A PHYSICIAN: He may have a benign cyst of the third ventricle.

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MIGRANT GODDESS

SIR William Osler, Bart., then Senior Physician of Medicine in Oxford University, contributed to the twenty-fifth anniversary number of *International Clinics* in 1915 a philosophical essay entitled "The Coming of Age of Internal Medicine in America." *International Clinics* survived its quarter century and has continued to survive, under a succession of aliases — as *New International Clinics,* then simply *Clinics,* and since 1946 as the *American Practitioner*.

The reaching of its majority by American medicine was a protracted process, not like the dawn of a birthday, which with the rising of its sun gives legal status to that person's manhood; it began with the inauguration of the Association of American Physicians in 1886 and culminated sometime during the period whose ending was the occasion of the jubilee. Prior to then the training of the American physician had passed through three periods, each dominated by the currently ascendant school of European medicine. In the first period the colonials brought the traditions of the mother country to this continent and sent their sons back for their medical education to Edinburgh or to London, or even to Leyden and to Italy. The first half of the nineteenth century saw French medical culture in the ascendancy and Paris as the Mecca of medicine; the sixth to the eighth decade witnessed the rise of the Austrian and German influence, with its solid impact on the modern science.

Sir William had previously written, in the *Journal of the American Medical Association,* in 1908, a nostalgic account of a return visit to Vienna, thirty-four years after his student days in that city. It was as a student that he had walked the wards in company with Shattuck, Bradford, Cutler and Sabine, of Boston; the return visit, to the German Congress for Internal Medicine, was made in the company of his later friend and student, Joseph H. Pratt, also of the Massachusetts Bay Colony.

In the earlier report as well as in the later essay Osler dwells in semiseriousness on the migrant and almost vagrant habits of Minerva Medica, the goddess of medical knowledge, who "has never had her chief temples in any one country for more than a generation or two." It is in *International Clinics* that Sir William describes her wanderings.

> Minerva Medica is a fickle goddess. Within a century and a half her sceptre has been seen in England, France and Germany. It looks as if she might cross the Atlantic and take up her abode in the land of Morgan and Rush, Gerhard and Flint, Holmes and Mitchell, Pepper and Fitz. Centuries ago she handed the torch of science to her darlings, the Greeks, and by that light we still work. Never has it burned brighter than in these dark days, and never so bright in the United States as in the brief quarter of a century, the completion of which is celebrated by this number of the *International Clinics*.

Minerva Medica, as Osler, himself something of a wanderer, predicted, surely reached the Western Hemisphere, but no longer can it be said that her

scepter rules in any single land alone. Rather have her descendants become a hierarchy whose scientific regimen in every virile and receptive nation is based on mutual understanding, co-ordinated effort and a devotion to the laws of humanity.

BOSTON MEDICAL LIBRARY — A NEW ERA

THE Greater Service Program of the Boston Medical Library, a fund-raising campaign initiated by the trustees in 1953, was aptly named. Its success — $308,000 was raised — precipitated a series of developments in increased service that augur well for this country's third largest medical library.

Under the imaginative guidance of Dr. Arthur W. Allen, president of the trustees, and the devoted care of Dr. Henry R. Viets, librarian and acting director (since the death of Director James F. Ballard last May), the Boston Medical Library's aim to provide the ultimate in *service, availability* and *utility* is closer to practical realization than ever in its eighty-one years of basic service to medical science, teaching and practice.

Five additional stack levels, a new elevator in the stack wing, a modern and efficient periodical room in memory of Dr. Frank H. Lahey, a remodeled elevator in the administration wing and general improvements were financed by the funds raised during the Greater Service Program campaign.

In addition to its continual acquisition of the latest in medical books and periodicals and medical volumes of historical significance, the Library, through grants from the American Cancer Society (Massachusetts Division) and the Massachusetts Heart Association, has enhanced these specific collections and made them readily available in Holmes Hall. An additional grant from the Massachusetts Heart Association has been made for the establishment and maintenance of a cardiovascular reference collection in Holmes Hall.

In November, 1955, the trustees inaugurated a free mailing service for members. Under this new plan, the Library will cover the postage and insurance costs of books and periodicals mailed to members and returned by mail to the Library. This service has more than tripled the Library's mail orders.

The services are showing annual increases. Recorded attendance in 1953 was 16,061, and it reached 17,484 in 1955. Circulation figures for the same period were recorded as 73,211 and 74,506.

In 1955, 4,293 volumes were added to the Library's collection, bringing the total volumes in the collections to close to 230,000. Pamphlets on hand total 158,755, and the Library is currently receiving 1,241 periodicals and serials.

After the death of Mr. Ballard, the trustees established the James F. Ballard Memorial Fund, the proceeds of which will be used for an employees' pension plan. To date, $10,300 has been received from 397 contributors, and an additional $10,000 from two sources will be forthcoming shortly. Although this fund is off to a good start, it will have to be increased considerably if adequate pension plans are to be provided.

Plans for the Dr. Francis T. Hunter Museum are under way, and the Women's Committee of the Library will have a hand in its implementation.

The trustees have for some time felt the need for a substantial endowment fund, built up by a continuous flow of bequests, and have undertaken a program to stimulate and encourage substantial bequests. Two recent bequests and one known to be forthcoming indicate that, if not great, the expectations are at least encouraging.

On March 6, in a talk before seventy members attending the Library's annual meeting, Dr. Chester S. Keefer stressed the fact that, as a "great storehouse of intellectual capital," the medical library is an integral and basic part of medicine and that to be of service its contents must be available to all physicians.

On April 2, as mentioned elsewhere in this issue of the *Journal,* Charles C. Colby, III, will take over the general supervision of the Library and personnel at a time when its prospects of services have never been better. Backed by an enthusiastic board of trustees and headed by the well trained and experienced Mr. Colby, the Boston Medical Library is entering into a new era — one that, it is hoped, will see the complete fulfillment of the dreams of its founders and the wishes of its contemporaries as so ably expressed by Dr. Keefer.

HIBERNATION AND THE TOXEMIC STATE

BACTERIAL toxins can prove injurious to individual cells directly, as in diphtheritic myocarditis or neuritis. But in other cases, the toxins also lead to reflex or hormonal actions. Thus, one finds hyperpyrexia, tachycardia, diarrhea, vomiting and drowsiness — a picture clinically spoken of as a "toxemic state." If a patient can be relieved of these symptoms, he assumes a more restful and normal appearance and attitude; the antibiotics have a better opportunity to act, and the patient's own ability to build up antibodies is improved. When patients with toxic diarrhea have been given procaine intravenously, the change in their appearance has been described as a "veritable resurrection from the dead."[1] Although the toxins may still be lethal to the cells, the general toxemic appearance has disappeared.

Recently, another approach to overcome the toxemic state has been presented by Italian pediatricians; they made use of hibernation. Laborit, a French clinician, had initiated the work on artificial hibernation, accomplishing it by certain drugs that affect the various hormonal activities and vegetative nerv-

ous reflexes.[2] This state of hibernation is manifested by low body temperature, low metabolism, hypotension, slow respirations and pulse rates, glandular hyposecretion (thyroid, pituitary, salivary and gastrointestinal), slowed peristalsis, diminished urinary excretion, low azotemia, leukocytosis and low blood coagulability; the electrocardiographic waves are of low voltage (as in myxedema), and the electroencephalographic waves are those of sleep.

Crisalli, Scarabicchi and Terragna, of the Pediatric Clinic of the University of Genoa,[3] have reported 9 cases in infants forty-eight days to eleven months of age in marked toxemia from gastroenteritis. All of the infants had failed to respond to accepted methods of treatment; they were in extremis and apparently destined to die shortly. Some of the cases were complicated by mastoiditis, pneumonia or myocarditis. Each child was given the hibernation treatment. The drugs used — chlorpromazine (Thorazine, Largactil), promethazine (Fargan), Hydergine (Hydergin) and meperidine (Mephedin, Demerol) — were given intravenously in a glucose solution, the dose of each varying with the size of the child and the presenting symptoms. Largactil is an antispasmodic, produces hypothermia, acts on the vegetative nervous system and causes what may be called a "pharmacologic lobotomy." Fargan is an antihistaminic and an analgesic. Hydergin is a vasodilator, and thus contributes to a lowering of the body temperature. Mephedin was used with the older infants only for its analgesic effects. After the injection, the infants entered into a quiet sleep, passed little urine and had no bowel movements, even though they had had diarrhea. The body temperature gradually fell to about 89.6°F. (32°C.) and remained at that level. No ice packs or local applications were needed or used to lower the temperature. The pulse rate became 60 to 90, and the respirations 20 to 30. Careful watch over the infants was maintained so that untoward reactions could be counteracted. The antibiotic therapy was continued. Heparin was given together with 4 per cent glucose solution to combat any dehydration. Prostigmin was available if there was abdominal distention, as were barbiturates for convulsive tendencies. The infants tolerated the hibernation well, and it was allowed to continue for twenty-four to forty-eight hours. Feedings were gradually resumed after the end of the period. Seven of the nine infants recovered completely; 2 died some days later, 1 with myocarditis, and the other with mastoiditis.

References

1. Torricelli, C. Use of novocain hydrochloride intravenously in treatment of toxic syndromes of infants. *Il Lattante* **18**:603, 1947.
2. Laborit, H., and Huguenard, P. *Pratique de Hibernothérapie en Chirurgie et en Médecine*. 256 pp. Paris: Masson, 1954.
3. Crisalli, M., Scarabicchi, S., and Terragna, A. Artificial hibernation in pediatrics: its application in toxic infections of infants. *Minerva pediat.* **7**:1318, 1955.

MENDED HEARTS

The mutual comfort that is derived when two or three are gathered together has influenced the forming of many useful and productive associations. Physicians have long been accustomed to meet and discuss their common problems; similar exchanges among their patients are a relatively recent development based somewhat on the principles of group therapy although independent of direct and regular medical supervision.

Alcoholics Anonymous constitutes a spontaneous affiliation of this nature dedicated to the rehabilitation of those who are in dire need, and a society of ileostomy patients exists for mutual encouragement and the exchange of useful experiences.

A few years ago, under the encouraging name of the Mended Hearts, Incorporated, a small group of patients in Boston who had recovered from and benefited by heart surgery formed such an association. They were inspired by the fact of having been lifted out of a dead-end street and set once more on the highway of life. They wanted to share this feeling of spiritual as well as physical renascence and adopted as their cheerful if not utterly original slogan "It's great to be alive — and to help others."

The Mended Hearts, Incorporated, includes not only veterans of heart surgery who are rehabilitated or are being rehabilitated but also, as associate members, their interested relatives and friends. There is an enthusiasm about emerging from the valley of the shadow, and the last annual meeting in June, 1955, brought forth an attendance of 750, of whom 400 were veterans of cardiac surgery, ranging in age from nine to sixty-four.

A function of active members of the society is to visit patients anticipating or recovering from surgery of the heart (with the approval of their physicians); to lend encouragement as living examples of what can be accomplished; to hand on, as the doctor can hardly do, an appraisal of the emotional stress through which patients must so often pass alone. The society advises and helps on matters relative to diet and food products and in many ways serves in an ancillary capacity to the surgeon and cardiologist.

As the technics of medical practice become of greater actual value and at the same time more complicated, greater efforts must be made to bring the laity into closer contact with their meaning.

The King of Belgium has just created eighteen of the most distinguished physicians in his kingdom, knights of the order of St. Leopold.

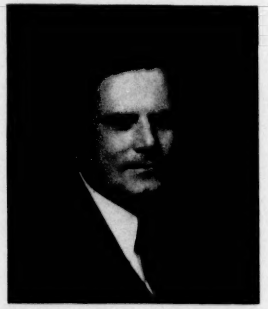
Boston M. & S. J., *April 3, 1856*

MASSACHUSETTS MEDICAL SOCIETY

HAROLD RICHARD KURTH, M.D.

It is the lot of some persons to be fully appreciated only when the depth of the void caused by death becomes apparent. Such a man was Dr. Harold R. Kurth, president-elect of the Massachusetts Medical Society, who died suddenly and quietly at his home on the afternoon of February 7, 1956, thus ending at sixty years a life of tireless devotion and service to his patients, his associates, the Lawrence General Hospital and the Massachusetts Medical Society.

After his preliminary education at Phillips Andover Academy, he received his A.B. degree *cum laude* from Harvard College in 1915 and his M.D. degree from Harvard Medical School in 1919. He naturally re-



turned to Lawrence and the Lawrence General Hospital, where his brother already was an established and respected surgeon, for his internship of one year, after which he established his general practice in 1920. His appointment to the staff of the Lawrence General Hospital followed in 1921. Shortly thereafter he assumed the responsibilities of medical director of the Pacific Mills in Lawrence, a position he held until his death. He was appointed to the senior staff in surgery at the Lawrence General in 1937, a post earned by a rapidly growing and successful surgical practice, and in 1943 he became president of the staff and chief of the Surgical Service, posts he still held at the time of his death. During the war years, he successfully bore the brunt of surgical practice in Lawrence and then in 1947 and 1948 was the prime mover in the much needed reorganization of the staff of the hospital to ensure in that hospital the highest type of medical and surgical care that the practitioners in the community could provide and to encourage those who could provide better service to establish practices there. At his death, he had just seen successfully completed the raising of funds for a new wing on the hospital, a project undertaken largely because of the faith and courage of the staff he so ably and unobtrusively directed.

His service to the Massachusetts Medical Society has been long, faithful and effective. He was a councilor from 1936 to 1939, Public-relations councilor from 1944 to 1955, secretary to the Committee on Public Relations from 1947 to 1955, secretary of Essex North District Medical Society for twelve years (1939 to 1951) and alternate delegate and delegate from Massachusetts to the House of Delegates of the American Medical Association in 1954 and 1955. Finally, recognition of his service was accorded him in 1955 by election as president-elect of the Society. Characteristically, he had recently devoted himself wholeheartedly to familiarizing himself with his new responsibilities and incidentally had made himself a capable and effective public speaker.

He was long a fellow of the American College of Surgeons and more recently fellow of the International College of Surgeons and honorary fellow of the International Academy of Proctology. He was a thirty-second-degree Mason of the Aleppo Temple and a member of the Aesculapian Club of Lawrence and the Harvard Club of Boston.

In 1921 he was married to Bessie D. Nieley, R.N., who survives him with three children: Major H. Richard Kurth, U.S.M.C., presently a White House aide; First Lieutenant Wilfred Kurth, U.S.M.C.; and Mary Jane Longabaugh, wife of Dr. Edward Longabaugh, of Rochester, New York.

Dr. Kurth will long be remembered for his devoted and skillful surgical care, his staunch loyalty to his friends when their need was greatest, his unhurried willingness to listen to the many who sought his counsel, his quiet patience and dogged perseverance in support of all that meant better medical care in his community, his generous material aid to many less fortunate or temporarily unfortunate practitioners and his restraint in the face of occasional bitter or unwarranted criticism. Osler's "Aequanimitas" might well be his epitaph.

D. W. W.

BOSTON MEDICAL LIBRARY

THE NEW LIBRARIAN

On April 2, Charles C. Colby, III, who for five years served as reference librarian at the Boston Medical Library before accepting, in September, 1954, the post of medical librarian and assistant professor of

medical bibliography at the University of Missouri, will assume the position of librarian for the Boston Medical Library.

Eminently well trained and experienced in medical librarianship, Mr. Colby will return to the institution to which he gave so much of his energies and talent to carry on and develop even further the "new look" of increased services sparked by Dr. Arthur W. Allen, president, and Dr. Henry R. Viets, who has served the Library so well as librarian over the years, and especially as its director during the interim resulting from the death of Mr. Ballard and the subsequent appointment of Mr. Colby.

Mr. Colby graduated from Harvard College in 1945, and in 1947 received his B.S. degree in library science from Simmons College. Before coming to the Boston Medical Library in 1949, he served as a subject cataloguer with the Army Medical Library.

In 1950, as a specialist in medical libraries with the State Department, office of the High Commissioner for Germany, he made a general survey of the medical-library facilities and resources in Western Germany, examined medical-library collections in the Amerika Haüser and other United States agencies in Germany, studied the programs of the several governmental and nongovernmental organizations that were donating medical books and periodicals to German libraries and advised the High Commissioner's office concerning improvements in the program to aid medical libraries.

A contributor to several professional publications, Mr. Colby is a member of the Medical Library Association and Special Libraries Association and has served as business manager of the *Bulletin of the Medical Library Association.*

NOTICES

SEMINAR ON HUMAN CANCERS

A seminar on the subject "Observations on Growth Rate of Human Cancers," sponsored jointly by the Cancer Research Institute of the New England Deaconess Hospital and the Children's Cancer Research Foundation of the Children's Medical Center, will be held in the Joslin Auditorium, New England Deaconess Hospital, Boston, on Tuesday, April 3, at 4 p.m. The speaker will be Vincent P. Collins, M.D., of the Department of Radiology of Baylor University College of Medicine.

NEW YORK ACADEMY OF SCIENCES

A meeting of the New York Academy of Sciences will be held at the Barbizon-Plaza Hotel, New York City, April 6-7. The session on physics and chemistry will be held Friday, 9 a.m. until noon, and the session on pharmacology and toxicology will be held in the afternoon from 2 to 5 p.m. The final session on clinical medicine is scheduled for Saturday, from 9 a.m. to noon. Further information may be obtained from The New York Academy of Sciences, 2 East Sixty-Third Street, New York 21, New York.

HARVARD MEDICAL SOCIETY

A symposium on the subject "Protein Formation and Growth," sponsored by the Harvard Medical Society, will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, April 10, at 8 p.m. Dr. Paul C. Zamecnik will preside. The program is as follows:

The Machinery of Protein Synthesis in the Ehrlich Ascites Tumor. John Littlefield and Elizabeth Keller.

Metabolic Control of Enzyme Biosynthesis in Bacteria. Boris Magasanik and Frederick C. Reidhardt.

Hypocaloric Dwarfism. John D. Crawford.

Protein Depletion and Wound Healing. Leon C. Edwards and J. Englebert Dunphy.

SOCIETY MEETINGS AND CONFERENCES

April 2. Fried Lecture Series. Page 535, issue of September 22.
April 2. Benjamin Waterhouse Medical History Society. Page 539, issue of March 15.
April 2 and 16. Hartford Medical Society. Page 242, issue of February 2.
April 3. Third Microcirculatory Conference. Page 399, issue of February 23.
April 3. Boston City Hospital House Officers' Association. Page 297, issue of February 9.
April 3. Seminar on Human Cancers. Notice above.
April 4. New England Surgical Society. Page 347, issue of February 16.
April 5. Second Annual Symposium on Cardiovascular Disease. Page 490, issue of March 8.
April 6. Massachusetts Society of Anesthesiologists. Page 539, issue of March 15.
April 6 and 7. New York Academy of Sciences. Notice above.
April 7. American Congress of Physical Medicine and Rehabilitation. Page 491, issue of March 8.
April 8. American College of Gastroenterology. Page 491, issue of March 8.
April 10. Harvard Medical Society. Notice above.
April 12. Nu Sigma Nu Fraternity. Page 491, issue of March 8.
April 15–20. American College of Allergists. Page 399, issue of February 23.
April 16–18. Aero Medical Association. Page 585, issue of March 22.
April 16–21. American Academy of Pediatrics. Page 399, issue of February 23.
April 18. Greater Boston Medical Society. Page 208, issue of August 4.
April 23–26. International Academy of Proctology. Page 399, issue of February 23.
April 25. Massachusetts Heart Association. Page 490, issue of March 8.
April 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
May 22–24. Massachusetts Medical Society Annual Meeting.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 5

THURSDAY, APRIL 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Hemodynamics of Aortic Stenosis. Dr. Hiroshi Kuida. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, APRIL 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

(Continued on page xx)